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BLECKMANN, K. H., and SALUS, D. (Kinderklin. d. Städt. Krankenanst., Essen, Germany), Beitrag zur Schlafmitteltherapie im Kindesalter. Erfahrungen mit Glutarsäureimid als Schlaf- und Beruhigungsmittel. *Med. Mscr. (G.)* 10, 162, 1956.

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* T.M. Reg.



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YNGVE ÅKERRÉN

in memoriam

Professor Yngve Åkerrén, professor of Paediatrics at the University of Gothenburg, died on January 14th, 1957, aged 61 years. The cause of death was cancer of the lung, diagnosed only a few months earlier, but his health had been poor for several years.

Yngve Åkerrén received his medical education at Uppsala University, and there he acquired his basic experience in paediatrics and general medicine. In 1934 he defended his thesis, *Experimental Changes in Liver Function—A Contribution to the Diagnosis of Liver Function*, in which he described investigations on liver function in carbohydrate deficiency, and came to the conclusion that an adequate glycogen reserve is essential for the proper functioning of that organ.

In 1931 he had been appointed senior physician to one of the first non-university departments of paediatrics in the country, at Linköping. In 1944 he succeeded Wallgren as senior physician to the Children's Hospital, Gothenburg. In 1954 he became the first occupant of the chair of paediatrics at the University of Gothenburg.

Åkerrén had an unflagging enthusiasm for medical research. Even as hospital physician with a heavy burden of clinical work he was constantly engaged in research, and, during the last decade of his life, when greater facilities became available to him, he made considerable achievements. He was the leader of a group investigation into the causes of perinatal mortality. With able collaborators he devoted a great deal of attention to the care of premature infants, and introduced radical therapeutic methods that resulted in a lowering of the mortality. By developing Ylppö's method of intragastric oxygenation Åkerrén and his collaborators arrived at a recognized technique for the treatment of initial asphyxia which has become internationally applied. Many Gothenburg families will long remember Åkerrén's work for children with cerebral palsy. To anyone who saw him at the school for spastics there, his genuine affection for these young patients was obvious.

Åkerrén was a capable administrator, a quality which stood him in good stead both in his work as hospital director and in prophylactic child care. He was convinced of the paramount importance of prophylaxis, and it was a source of great satisfaction to him to note the striking fall in Swedish infantile mortality that accompanied the ever-intensifying child welfare work.

It was a joy to discuss scientific problems with Åkerrén. He loved to put a question, and would readily take up a critical, opposing attitude for the sake of argument. He made his point concisely and with authority, and his knowledge and clearness of thought were impressive. He had exceptional clinical acumen, and inspired confidence in students and patients alike. He was a stimulating teacher, a good doctor, and a noble representative of Scandinavian paediatrics.

From the Maternity Clinic, Sabbatsberg Hospital, Stockholm (Head: Prof. Per Wetterdal, M.D.) and The Wenner-Gren-Research Laboratory, Norrtull Hospital, Stockholm.

Technique and Estimation of Oxygenation of the Human Fetus in Utero by Means of Hystero-Photography¹

by BJÖRN WESTIN

Introduction

The oxygen consumption of the human fetus has been a subject of great interest. Its magnitude at different stages of fetal development was studied by Barcroft, Kennedy & Mason (1940) in animal experiments. In humans, the oxygen content of the cord blood has been determined in previable fetuses (Westin, 1955) and in mature newborns after spontaneous delivery and cesarean section (reviewed by Smith, 1951). If the results obtained after birth apply to intrauterine life, the fetus should be extremely hypoxemic at the end of gestation (Barcroft, 1946; Rooth & Sjöstedt, 1955). Operative procedures on the mother and even normal deliveries alter the placental circulation and may make the results obtained not fully representative of intrauterine life.

Determination of the oxygen consumption of previable human fetuses may also be done under conditions similar to those *in utero* by perfusing the fetuses with oxygenated heparinized blood (Enhörning & Westin, 1954) after delivery. Recordings of blood-flow and arterio-venous difference in oxygen saturation of the cord vessels indicate that the oxygen consumption of fetuses perfused in the fourth and fifth month of gestation is of about the same magnitude as in mature newborns (Westin, 1956). It was considered of interest to compare these results with what might be found *in utero*. For this purpose the hysteroscopic technique was chosen. A preliminary communication on this subject was given in 1954 (Westin). In the present paper the technique and some results are described.

¹ Paper presented on invitation at the Pediatric Clinic, Karolinska Sjukhuset, Stockholm, September 14, 1956.

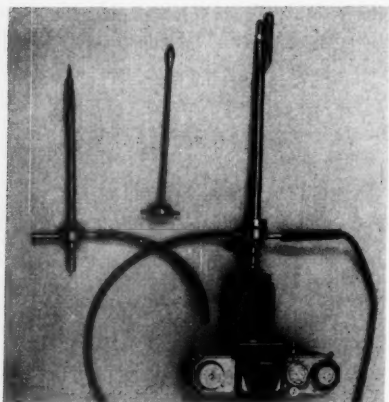


Fig. 1. The instrument for hystero-photography. From left to right: knife, obturator, the instrument mounted.

Technical Equipment

The hysteroscope consisted of an external tube having a diameter of 10 mm (Fig. 1). An obturator was used for introducing the hysteroscope to the fetal membrane. A knife inside the tube could be triggered for puncture of the fetal membranes. The optics of the instrument were of the same type as in the McCarty cystoscope. The instrument measured 5×300 mm and carried a pilot light. The opening of the optical system facing the camera was 2 mm. For illumination of the uterine cavity a krypton tube measuring 9×30 mm was used. This tube contained krypton having a pressure of less than 1 mm mercury. A potential of 500 v was applied on two electrodes from a condenser having a capacity of $400 \mu\text{F}$. The energy supplying a discharge in the tube was 200 w.-sec. The discharge was initiated through another electrode which was supplied with 5000 v. The current was of negligible magnitude. This voltage gave rise to ionization of the krypton gas and started the condenser discharge. By introduction of an inductance in the condenser discharge circuit, the discharge time was regulated to 0.02 sec, which was determined by means of photocell recordings.

The amount of light given at each discharge and the exposure time was thus standardized. Variations in illumination of the film during an exposure were due mainly to variations in distance between film and object. In order to estimate the influence of variations in film-object distance on the amount of light falling on the film during an exposure, the following experiment was performed. The film was replaced by a photocell and an opaque white disc was placed at different distances from the lens, which was kept close to the krypton tube. The current induced in the photocell during a single flash of the krypton tube was determined and plotted in a semi-logarithmic system against distance in mm (Fig. 2). A straight line relation was found indicating that a change in distance of ± 5 mm altered the amount of light falling on the photocell by 10 per cent, within the range of distances measured.

The photographic pictures were taken using a mirror reflex camera (Trade mark Edixa). The focal distance of the objective was 10 cm. The camera was mounted directly on the optical system of the hysteroscope. The operator could look through the hysteroscope except during the taking of a photograph. The colour film used was

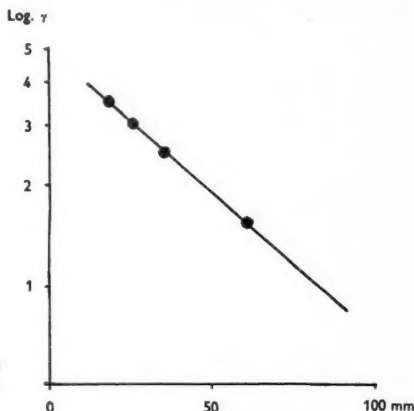


Fig. 2. Amount of light recorded by the photocell in relation to lens-object distance. Y = amount of light per unit time.

Ansco-Chrome 135, Daylight of 17 degrees Din and developed under prescribed standard conditions.

The light of the krypton tube had a bluish colour: the colour sensitivity of the photographic emulsion to this light was investigated using a filter to make the light isoenergetic. This light source was compared to a standard isoenergetic light source E (nomenclature of David & Gibson, 1934) by making wedge spectrograms, recorded on the Ansco-Chrome film (Bäckström, 1953).

The total radiant energy falling on the film was approximately the same in both cases. The spectrogram showed the sensitivity to light as a function of the wavelength. Using light source E , the sensitivity was approximately uniform in the blue, green and red wavelengths. A different relation was found when light from the krypton tube was used. The sensitivity in the blue range was approximately twice that in the red (Fig. 3). The conclusion can be drawn that the intensity (log) of light from the krypton tube in the blue range was approximately twice that in the red.

We have now investigated variations in film-object distance, the sensitivity of the photographic emulsion and the light source used in the present experiments. On the same colour film photographs of the cord vessels taken *in utero* were compared with similar photographs of cord vessels taken outside the uterus in order to compare oxygenation of blood. In the first instance amniotic fluid acted as a light filter; in the second instance normal saline was substituted; the spectral absorption curve of the two fluids were compared in a Beckman quartz spectrophotometer. Distilled water was used as standard. The optical density of normal saline was 0.004 between 3.750 and 6.750 ÅU. The density of the amniotic fluid is indicated in Fig. 4. The mean optical density for a 20 mm thick layer of the amniotic fluid (twice the distance between lens and object) was 0.12 in the red range and 0.48 in the blue. The amniotic fluid therefore acted as a red filter. This gave a calculated mean transmission of 76 per cent in the red range of wavelength and of 33 per cent in the blue.

The introduction of amniotic fluid as a filter between lens and object reduced the disproportion in sensitivity (log) of the photographic emulsion in the blue and red wavelengths from 2:1 to 1.6:1. Nevertheless, this resulted in a false apparent bluish

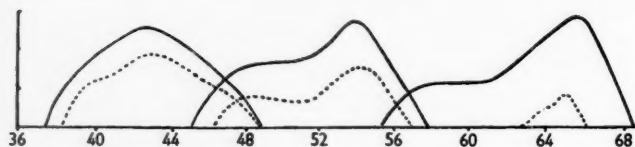


Fig. 3. Iso-energetic wedge-spectrograms. Drawn in the darkroom at $5\times$ magnification. Ordinate = sensitivity (log). Abscissa = $AU \times 10^{-2}$. —, light source E. ---, krypton tube

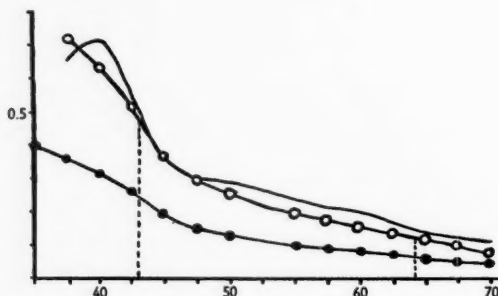


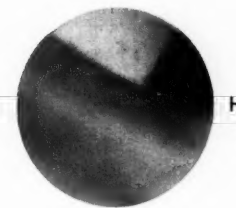
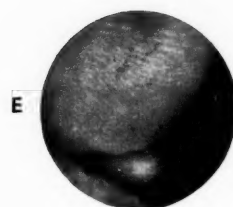
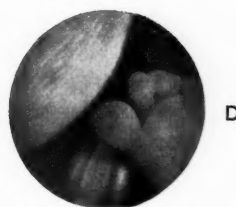
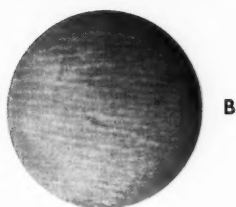
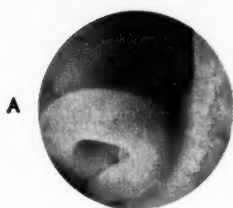
Fig. 4. Density of the amniotic fluid and of the light filter used. Ordinate = density (log). Abscissa = $AU \times 10^{-2}$. ---, 10 mm layer of amniotic fluid (lens-object distance). -o-o-o-, 20 mm layer of amniotic fluid. —, two layers of Kodak Wratten filter 81 B. ---, mean optical density in the blue and red wavelengths.

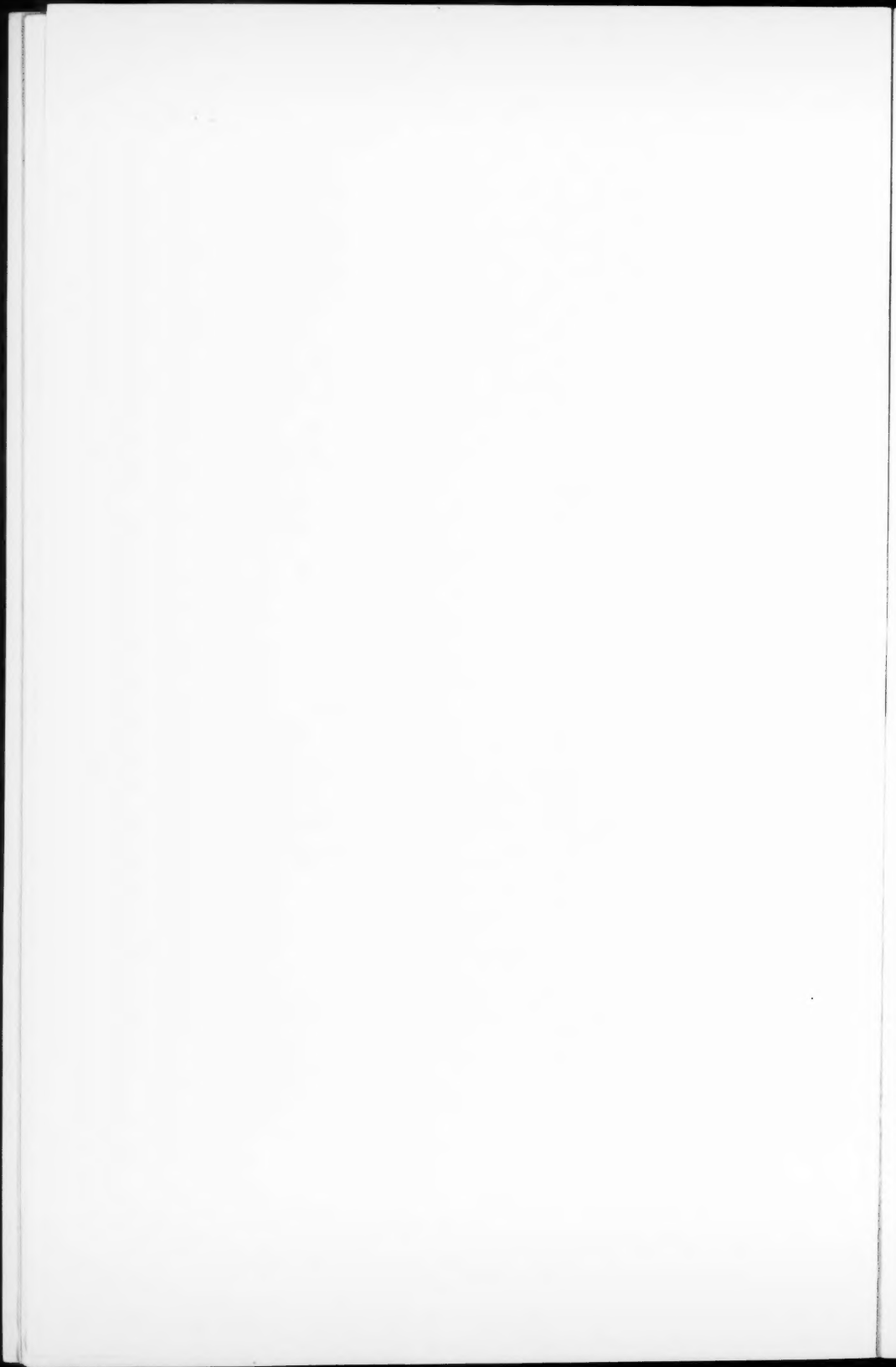
colour of the intrauterine photographs, which was of no importance when intrauterine photographs were compared with one another.

Photographs taken in normal saline had to be corrected to be comparable with photographs taken in the uterus. Assuming a rectilinear colour density curve and a γ -value = 1 in the blue and red wavelengths (which is very close to the fact in reversal daylight colour films), the colours of the photographs taken in normal saline could be corrected at the examination by means of a filter. This filter (2 layers of Kodak Wratten, Light filter 81 B) had a density corresponding to the density of twice the layer of amniotic fluid between lens and intrauterine object (Fig. 4).

Fig. 5. A-G, uncorrected intrauterine photographs. H, photographed in normal saline and corrected with two layers of Kodak Wratten filter 81 B.

A, the ear and one upper limb of the fetus. B, detailed view of the fetal skin: note gland openings. No cutaneous cyanosis. C, central part of the fetal placenta. In the background the heel of the fetus is seen. D, no cyanosis of the toes of the fetus. No difference in colour between toes and head in spite of difference in film-object distance. Note difference in colour between umbilical vein and arteries. E, the placenta at the left margin and part of the body at the top of the picture. Note difference in colour between umbilical vein and artery. F, close view of the umbilical cord. Note reflexions obscuring the true colour of the umbilical arteries. G, umbilical vein at 10 mm distance *in utero*. H, corrected photograph of resected piece of the umbilical cord in Fig. 5G, perfused with oxygenated (umbilical vein) blood.





Material and Operative Procedure

The investigations were made on patients who were to have therapeutic abortion. The length of pregnancy was about 14–18 weeks. No morphine was given preoperatively. The anaesthesia was about 15 ml 0.25 per cent xylocain-exadrine, locally in the uterine cervix.

The hysteroscope was inserted into the uterine cervix after dilatation to Hegar 10. The knife for puncture of the fetal membranes was inserted. The instrument was filled with normal saline at 37°C and under pressure of about 50 cm of water. The inflow was closed and the membranes were sucked into the hysteroscope by means of a syringe connected with the system. Thereafter the knife was triggered and the membranes punctured inside the hysteroscope. The sign of successful puncture was immediate refilling of the connecting tubes of the water system. The knife was removed and the krypton tube and the optical system were introduced. Photographs were taken during continuous washing of the lens with normal saline at 37°C.

Results

Vision was extremely good inside the fetal membranes and permitted detailed examination of the fetus, the placenta, and the umbilical cord.

The skin of the fetus was examined in various sites, particularly the ears (Fig. 5A), nose, fingers and toes (Fig. 5D) in order to see if cyanosis was present. No cutaneous cyanosis was seen and the fetus appeared much pinker than fetuses of comparable size after delivery. Fine details such as gland openings in the skin could be distinguished (Fig. 5B).

The placental surface appeared much less cyanotic than after delivery. The central part bulged into the uterine cavity (Fig. 5C). Upon closer examination arteries and veins could be distinguished by their colour difference.

The umbilical cord was photographed at different distances between lens and object within the uterus (Fig. 5D–G). The pink umbilical vein contrasted sharply with the blue arteries. Light reflections in the Wharton's jelly sometimes obscured the true colour of some of the vessels (Fig. 5F).

After hysteroscopy a section of the umbilical cord was resected and used for perfusion experiments. The vein was perfused with oxygenated heparinized blood and one artery was perfused with venous blood drawn from the same donor. Photographs were taken through normal saline at approximately the same distance as those *in utero*. After correction of the photographs taken in normal saline, the colours of the cord vessels were approximately the same under both conditions (Fig. 5G and H).

Postoperative Complications

In hysteroscopies performed in gynaecologic cases (Englund, Ingelman-Sundberg & Westin, 1956) it was found that hysteroscopy did not increase the complications following curettage. In eight hysteroscopies performed in early pregnancy the postoperative course was without complication. In a ninth case a uterine blood vessel was cut when the membranes were punctured but only minor bleeding occurred and stopped spontaneously. This accident was thereafter avoided by puncturing the membranes within the hysteroscope.

Discussion

Direct visualization of the umbilical vessels *in utero* indicates that the oxygenation of the human fetus is high during the 14–18th weeks of gestation. These findings agree with those obtained in perfusion experiments on previable human fetuses (Westin, 1956). Cyanosis of the fetus and placenta after delivery in therapeutic abortions suggests that the oxygen content of the cord vessels is lower after delivery than during intrauterine life. In these nonbreathing fetuses continuing metabolic demands rapidly reduce the oxygen concentration (Westin, 1955). The hysteroscopic technique opens new possibilities of obtaining information on the physiology of the fetus. Studies on intrauterine ECG and direct determination of the fetal oxygen tension are in progress.

Acknowledgements

The author gratefully acknowledges the co-operation of photographer Lennart Nilson both in technical assistance and in covering the cost of the equipment, of civil engineer Werner Donné in designing the technical equipment, of Professor Helmer Bäckström, assistant Anders Kajland and of civil engineer Torbjörn Koch, Department of Photography, Royal Institute of Technology, Stockholm, Sweden, in making available the necessary photographic instruments and for valuable advice in treating some of the results, and finally of the "Association for the Aid of Crippled Children" in financing the publication of this paper.

Summary

A technique is described for hystero-photography of the intrauterine fetus. A krypton tube was used for illumination. Details of the fetus, umbilical cord and placenta were examined and photographed in colour. The umbilical vein was seen to be pink and the arteries blue. The oxygenation of the umbilical vein was estimated to be high. This estimation was based on comparison between intrauterine photographs and photographs of cord vessels perfused with blood of known oxygen saturation. The skin of the fetus was pink and numerous gland openings could be

seen. No cutaneous cyanosis was visible. Details of the placental surface and its circulation were clearly discernible and the organ appeared less cyanotic than after delivery.

Technique et estimation de l'oxygénation du fœtus human in utero au moyen de l'hystéro-photographie.

Description d'une technique d'hystéro-photographie du fœtus in utero. Illumination par tube à décharges électroniques. Evaluation de l'erreur d'illumination du film due aux variations de la distance focale du film. Des spectrogrammes en coin montrèrent que le tube électronique émet de la lumière avec prépondérance pour le champ bleu de longueur d'onde. Des densimétries d'eau physiologique et de liquide amniotique indiquèrent que le liquide amniotique sert de filtre rouge. On peut corriger cette erreur quand on évalue la saturation en oxygène des vaisseaux du cordon. Les détails du cordon ombilical du fœtus et du placenta sont examinés et photographiés sur des films en couleurs. On estime que l'oxygénation de la veine ombilicale est élevée. Cette détermination est basée sur la comparaison de photographies intra-utérines et de photographies des vaisseaux ombilicaux dans lesquels on avait injecté du sang de teneur en oxygène connue.

Ein Verfahren zur Schätzung der intrauterinen Sauerstoffzufuhr beim menschlichen Foetus mit Hilfe von Hystero-Photographie.

Eine Methode zur intrauterinen Hystero-Photographie des Foetus ist beschrieben. Zur Belichtung wurde eine Elektronenröhre verwendet. Die Abweichung in der Film-belichtung in Abhängigkeit von Unterschieden der fokalen Distanz wurde abgeschätzt. Keilspektrogramme zeigten, dass die von der Elektronenröhre ausgehenden Strahlen ein Überwiegen im blauen Wellenlängenbande aufwiesen. Densitometrische Untersuchungen von physiologischer Kochsalzlösung und Amnionflüssigkeit wiesen darauf hin, dass die letztere als Rotfilter wirkt. Eine Berichtigung dieser Abweichung kann durch eine Schätzung der Sauerstoffsättigung im Blut der Nabelschnurgefäße gemacht werden. Einzelheiten der Foeten, Nabelschnur und Placenta wurden studiert und in farbigen Photographien dargestellt. Die Schätzung ergab hohe Werte für den Sauerstoffgehalt in der Nabelvene. Die Berechnung beruhte auf einem Vergleich zwischen Photographien von intrauterin beobachteten Nabelschnurgefäßen und anderen Nabelgefäßen, die von Blut mit bekannter Sauerstoffsättigung durchspült waren.

Técnica y estimación de la oxigenación intrauterina del feto humano por medio de la histerofotografía.

Describe una técnica histerofotográfica intrauterina del feto. Utilizóse para la iluminación un tubo de descarga electrónica. Estimóse el error de iluminación en la película con motivo de las variaciones de la distancia del enfoque pelicular. Cuñas espectrográficas indicaron que el tubo electrónico desprendía luz con preponderancia para el campo azul de onda longitudinal. La densimetría del líquido normal salino y amniótico indicó que el líquido amniótico actúa como un filtro rojo. Puede hacerse la corrección de este error por estimación de la oxigenación de los vasos del cordón. Se fotografiaron en películas de color y se examinaron detalles del cordón umbilical del feto y de la placenta. La oxigenación de la vena umbilical se estimó era elevada. Fundóse esta estimación en una comparación entre fotografías intrauterinas y fotografías de vasos del cordón perfusionados con sangre de oxigenación conocida.

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Staphylococcal Epidemiology in a Maternity Hospital

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Introduction

The prevalence of *Staphylococcus aureus* infection amongst infants, the not infrequent occurrence of severe sepsis and the emergence of polyantibiotic resistant strains of the organism, has resulted in many studies in staphylococcal epidemiology in maternity hospitals.

The conclusions reached in a number of accounts are contradictory, whilst frequently the published data are either insufficient or open to more than one interpretation. Allison & Hobbs (1947) concluded that a prerequisite of infant infection was a rise in the nasal incidence of a particular strain in the nursing staff, a conclusion which fails to explain why during their "pemphigus" epidemics occasional cases arose due to strains of "foreign" type in which the "prerequisite" state of affairs did not obtain. On the other hand Parker & Kennedy (1949) found that cases of "pemphigus" continued to occur when no nasal carrier of the epidemic strain could be demonstrated in the nursing staff.

Available data from maternity units has been confused by finding of many serological and 'phage types of *Staph. aureus*. Allison & Hobbs (1947) noted 7 serological types; Parker & Kennedy (1949) recovered 10 'phage types; Rountree & Barbour (1950) found 14 'phage patterns; Wallmark & Laurell (1952) recognised at least 10 'phage types and Barber, Wilson, Rippon & Williams (1953) 11 'phage types. In these cases the published data are insufficient to assess the position of individual types in relation to the total picture of staphylococcal hospital flora, and little is known of any week-to-week variation of type incidence.

Several workers have noted the similarity of nasal carriage rates of penicillin-resistant *Staph. aureus* between nurses and the infants under their care (Rountree & Barbour 1950; Barber *et al.* 1953). However, Forfar,

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Balf, Elias-Jones & Edmunds (1953) showed that resistant carrier rates of nurses and infants, for antibiotics other than penicillin, bore singularly little relation to each other.

The transmission of the mother's nasal *Staph. aureus* to her infant appears to be an uncommon occurrence. Parker & Kennedy (1949) cite an instance and a further possible case was found by Rountree & Barbour (1950). Allison & Hobbs (1947), Cunliffe (1949) and Ludlam (1953) could find no evidence of such transmission. It therefore seems strange that infants should acquire nurses' nasal strains (Allison & Hobbs, 1947) yet the intimate contact necessitated in breast feeding, fails to promote similar acquisition from the mother.

Technical difficulties have no doubt been largely responsible for the lack of detailed knowledge. Though suggestive results have been obtained by sporadic or random sampling, usually in relation to already established disease, the maternity hospital environment seemed to warrant a more detailed study than has been made to date. It was therefore decided to carry out an intensive investigation for 3 months to elucidate some of the problems posed above.

Sources of Material Studied

The study was carried out in a small isolated maternity hospital in which 4 wards were examined. Wards 1 and 2 were topographically comparable in every way and were lying-in wards for 18 mothers with babies in cots at the bedside. Ward 5 (25 beds) was reserved for women with pregnancy complications and was regarded as a control of women without babies. In the Premature Nursery babies were isolated from their mothers.

Each ward had a core of permanent staff but most of the nursing was done by student midwives who moved from ward to ward in rotation every few weeks. The ordinary care of babies on Wards 1 and 2 was undertaken as far as possible by the mothers, except that the first 12 hours of life were spent in a small ward nursery.

Routine bacteriological specimens were obtained from the following sources:—

(1) *Infants*. Nasal and umbilical swabs from all infants, diseased or healthy, in the Premature Nursery, and on Wards 1 and 2 on one day each week.

(2) *Mothers* on admission. Nasal swabs from all women within a few minutes of entering hospital.

(3) *Mothers* on discharge. Nasal swabs from all women discharged from Wards 1 and 2 (i.e. about 10 days after admission).

(4) *Antenatal Ward 5*. Weekly nasal swabs from all women. All those specimens which were taken at 10 days after admission were subsequently selected for comparison with discharge swabs (see para. 3 above).

(5) *Follow-up* nasal swabs were taken at the post-natal clinic 6 weeks after discharge on a number of women discharged with 'hospital strains' in their noses. In a

small number a home visit was made 6 months after discharge, nasal swabs being taken from all available members of the family.

(6) *Hospital Staff*. Weekly swabs were taken from all medical, nursing, ward staff and medical students on Wards 1 and 2, the Labour ward, and Premature Nursery.

(7) *Dust*. During the latter half of the study dust specimens, obtained at weekly intervals were examined for *Staph. aureus*.

(8) *Infant Disease*. The onset of infant sepsis was followed by the immediate sampling of the lesion, the baby's nose, umbilicus, and mother's nose.

The total number of specimens obtained from the above sources during 13 weeks of study was 3542.

Methods

All specimens with the exception of some admission and discharge swabs were taken by one of us (W. D. B.) and were broth soaked before use. Staphylococci were isolated from salt meat broth (Maitland & Martyn, 1948) and coagulase-positive strains (Fisk, 1940) selected for 'phage typing (Williams & Rippon, 1952) and sensitivity tests (Hutchison, 1954). Strains were regarded as insensitive if resistant to penicillin 1 unit per ml and to streptomycin, chloromycetin and terramycin, 10, 20 and 4 mcg per ml respectively.

Dust samples were examined by decimal dilution of a known amount of material, a rough estimate of the number of staphylococci being obtained.

For convenience in treating the results, each 'phage pattern in which reactions were such that the strains could be regarded as representing a distinct population (Williams & Rippon, 1952), was given a code letter. Details of these reactions are given in the Appendix.

Bacteriological Findings

NASAL SWABS OF MOTHERS ON ADMISSION AND DISCHARGE

Admission.—The total of 554 swabs taken from women on admission were divided into 2 groups, 189 from Ward 5 (antenatal), and 365 from admissions to the Labour Ward and all lying-in wards.

Discharge.—There were 318 nasal swabs from mothers on discharge from Wards 1 and 2, and 87 from women on Ward 5, taken at 10 days.

Tables 1 and 2 compare 'phage type and antibiotic sensitivity of strains from the above groups.

(1) *Nasal carriage rate for Staph. aureus*

On Wards 1 and 2 there was a highly significant increase from 46.6 % on admission to 63.2 % on discharge. On Ward 5 there was an increase from 41.8 % to 48.3 %—an insignificant change.

TABLE 1

Carriage rate and 'phage typing results of Staph. aureus from mothers' nasal swabs on admission and discharge, comparing Ward 5 with lying-in Wards.

	Total number swabs examined	<i>Staph. aureus</i> carriers %	Phage groups* of strains				
			I	II	III	U.C.	Not typable with phage filtrate at R.T.D.
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Admission Wards 1, 2, 3, 4	365	170	49	17	18	7	79
% of strains (a)		46.6%	28.8%	10.0%	10.6%	4.1%	46.5%
Discharge Wards 1 & 2	318	201	24	9	109	4	55
% of strains (b)		63.2%	11.9%	4.5%	54.2%	2.0%	27.4%
Admission Ward 5	189	79	19	10	15	1	34
% of strains (c)		41.8%	24.1%	12.7%	19.0%	1.2%	43.0%
Discharge Ward 5	87	42	11	5	10	0	16
% of strains (d)		48.3%	26.2%	11.9%	23.8%	—	38.1%

*Phage Group I —52
 II —3A
 III —6/47
 U.C.—Unclassified

(2) Antibiotic sensitivity reactions

On Wards 1 and 2 an increase took place in penicillin-resistant strains from 14 % to 60 %, and streptomycin-resistant strains from nil to 41.8 % on admission and discharge respectively. No comparable change was seen on Ward 5.

(3) 'Phage reactions

The increase in 'phage Group 3 strains from 10.6 % on admission to 54.2 % on discharge from Wards 1 and 2 was significantly greater than the increase from 19 % to 23.8 % found on Ward 5.

There were therefore highly significant increases in the nasal carriage rate, and the carriage of antibiotic resistant 'phage Group 3 strains in

TABLE 2

Sensitivity patterns of Staph. aureus strains from mothers' admission and discharge nasal swabs, comparing Ward 5 with lying-in wards.

	Total strains	Number of strains of <i>Staph. aureus</i> with the following Sensitivity reactions*					
		P. } S. } C. } T. } s	P.—r } S. } C. } T. } s	P. } S. } C. } T. } r	P. } S. } C. } T.—s r	P. } S. } C.—s T.—r r	P.—s } S.—r } C. } T. } s
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Admission Wards 1, 2, 3, 4	170	146	24	0	0	0	0
% of strains (a)		86.0 %	14.0 %	—	—	—	—
Discharge Wards 1 & 2	201	79	39	60	14	8	1
% of strains (b)		39.4 %	19.3 %	29.9 %	6.9 %	4.0 %	0.5 %
Admission Ward 5	79	67	9	1	1	1	0
% of strains (c)		84.8 %	11.4 %	1.3 %	1.3 %	1.3 %	—
Discharge Ward 5	42	32	7	3	0	0	0
% of strains (d)		76.2 %	16.6 %	7.2 %	—	—	—

*P.—Penicillin, S.—Streptomycin, C.—Chloromycetin, T.—Terramycin; s—sensitive, r—resistant.

mothers on Wards 1 and 2 during their 10 days in hospital; but no such changes in women after a similar period in Ward 5. The major environmental difference between these groups of patients was the presence of babies in the former two wards and their absence in the latter. The difference strongly suggests a connection between the presence of infants and the rapid change in maternal nasal strains of *Staph. aureus*.

INFANT ROUTINE SWABS

Excluding swabs taken at the time of infection 878 routine weekly nasal and umbilical swabs were taken from 439 babies.

TABLE 3

Antibiotic sensitivity patterns of Staph. aureus from the nose and umbilicus of infants on Wards 1, 2 and in the Premature Nursery. The latter strains are divided into those under and over 10 days old.

	Total strains	Pen. res.	Strep. res.	Chlor. res.	Terr. res.	P. S. C. T.) ^s	P.— S. C. T.) ^s	P. S. C. T.) ^r	P.— S. C. T.) ^r	P. S. C. T.) ^r	P.— S. C. T.) ^r	P.— S. C. T.) ^r
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Ward 1	no. 172	148	118	21	27	23	31	72	18	2	25	1
Nasal and umbilical swabs	%	86.0	68.8	12.2	15.6	13.4	18.0	41.9	10.4	1.2	14.5	0.6
(a)												
Ward 11	no. 192	174	125	32	20	17	50	79	26	5	14	1
Nasal and umbilical swabs	%	90.5	65.0	16.6	10.4	8.8	26.0	41.1	13.6	2.6	7.3	0.6
(b)												
Prem. Nurs.	no. 90	80	72	25	21	10	8	31	20	5	16	0
Under 10 days												
old n + u swabs	%	88.8	80.0	27.7	23.3	11.1	8.9	34.4	22.2	5.6	17.8	—
(c)												
Prem Nurs.	no. 142	141	122	49	29	1	19	53	40	9	20	0
Over 10 days												
old n + u swabs	%	99.3	85.9	34.5	20.4	0.7	13.5	37.3	28.1	6.3	14.1	—
(d)												
Total	no. 596	543	437	127	97	51	108	235	104	21	75	2
(e)	%	91.1	73.3	21.3	16.3	8.6	18.1	39.5	17.4	3.5	12.6	0.3

(1) *Nasal and umbilical carriage rates for Staph. aureus*

Nasal and umbilical carriage rates increased in parallel, rapidly from birth to the 3rd day of life, 77.2 % at each site, and thereafter took on a more gradual climb to a maximum of 85.9 % at each site in the age group 7th–18th day. Swabs taken from 19th–46th day showed a slight but not significant decrease.

(2) *Antibiotic sensitivity reactions*

Table 3 gives the antibiotic sensitivity patterns of the 596 strains of *Staph. aureus* isolated. Infants on the Premature Nursery were divided into 2 groups, 10 days and under, and over 10 days of age when swabs were taken. The former group was thus of comparable age to the infants on Wards 1 and 2. There was only one (0.7 %) penicillin sensitive strain

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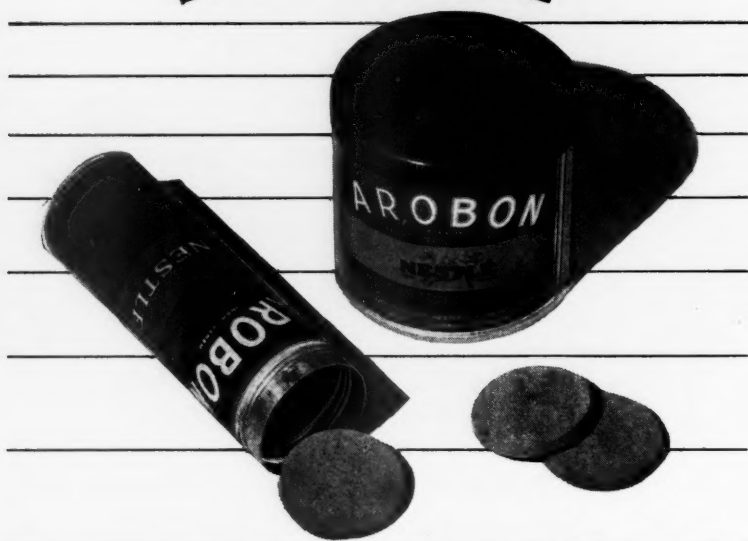
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TABLE 4

'Phage grouping and carriage rates of Staph. aureus from infant routine and umbilical swabs on Ward 1, 2 and in the Premature Nursery.

Ward	Total number swabs examined	Staph. aureus Carriers %	'Phage groups of strains			
			1	2	3	Not typable with 'phage filtrates at R.T.D.
1	280	172 61.4 %	23 13.4 %	1 0.6 %	128 74.4 %	20 11.6 %
2	288	192 66.7 %	22 11.5 %	2 1.0 %	144 75.0 %	24 12.5 %
Premature Nursery	310	232 74.8 %	6 2.6 %	0 —	210 90.5 %	16 6.9 %
Grand total of all wards	878	596 68.6 %	49 8.3 %	3 0.5 %	482 81.0 %	60 10.2 %

isolated from the Premature Nursery from infants over 10 days old, compared with 13.4 %, 8.8 % and 11.1 % in Wards 1, 2 and Premature Nursery under 10 days old. The latter 3 percentages were significantly higher than the former. On all wards the number of antibiotic-resistant strains, particularly to penicillin and streptomycin, was large.

(3) *'Phage typing results. Table 4*

There was a marked predominance of 'phage Group 3 strains from Infant Routine Swabs (81 % of all strains); and a significantly higher incidence of this 'phage Group in the Premature Nursery (90.5 %). Conversely 'phage Groups 1 and 2 strains were scanty in Wards 1 and 2 infants and their incidence in the Nursery was even lower. In the Nursery the scarcity of Group 1 strains was not tied to age distribution of infants as in the case of the penicillin sensitive strains.

The high incidence of penicillin-sensitive 'phage Group 1 strains in mothers on admission gives a clue to the differences between babies on the lying-in wards and the Nursery but on only 4 occasions was transfer from the mother to her infant proven. The difference in the incidence of penicillin-sensitive strains from Nursery babies under and over 10 days old suggested the acquisition of sensitive strains from the mother in the Labour Ward and this was shown in one instance. In this case, whilst vaginal carriage was not excluded, mother-baby contact was minimal before the child was sent to isolation in the Nursery.

The Bacteriology of Neonatal Sepsis

During the 13 weeks of study 157 specimens were taken from infant infections, 64 being "pustules" and 93 "sticky-eyes".

Pustules

Of the 64 pustules, 55 (85.9 %) yielded *Staph. aureus*, 6 (9.4 %) *Staph. albus* and from 3 no organism was isolated. The latter 3 were all pin-point lesions and failure to obtain cultures was ascribed to deficient sampling technique. The occurrence of *Staph. albus* might also have been explained on similar grounds had not several such lesions produced a relatively large amount of pus for culture, it was concluded, in these cases at least, that *Staph. albus* was the aetiological agent. *Staph. aureus* was isolated from 25 "pin-point" lesions and from 30 of 1 mm in diameter or larger. The results indicate that even minute lesions were associated with and presumably caused by *Staph. aureus* or occasionally by the *albus* (coagulase-negative) variant.

Sticky-eyes

Cultures from 93 "sticky-eyes" gave widely different results from those of the pustules. From 46 (49.5 %) *Staph. aureus* was isolated: from 31 (33.3 %) *Staph. albus* or some other organism (from one case anthracoid from another yeasts), and from 16 (17.2 %) "no growth" was obtained.

All those specimens giving "no growth" were from lesions from babies under 48 hours old. From babies in the 0-24 hour age group half the cultures gave "no growth", this finding was independent of the clinical severity of the condition, some extremely purulent eyes coming into this category. Gram-stained films of pus from these eyes showed leucocytes only. Inclusion body studies were not done.

The findings cast serious doubt on the bacterial aetiology of those "sticky eyes" arising in babies of the 0-48 hour age group. Two possible alternatives remain: (a) a chemical conjunctivitis, the antiseptic creams used during labour would seem to be the most likely; and (b) a viral pathogenesis; inclusion blenorrhoea seems to be unlikely in babies 24 hours old, yet "sticky-eyes" were more prevalent, in common with other infections in the Pre-mature Nursery. This fact of itself, would suggest an infective process with an incubation period of as little as 12 hours; at the same time the premature or injured infants may be more susceptible or more subject to irritants than others.

A comparison of results from 'sticky-eyes' and Infant Routine nasal and umbilical swabs showed that in both cases the finding of 'no growth'

occurred more frequently in the 0-24-hour age group than in later life: likewise the incidence of *Staph. aureus* and *albus* followed a parallel course. These findings suggest that the bacteria found in 'sticky-eyes' might have been merely secondary invaders of some other pathological process. It is of interest that Barber, Hayhoe & Whitehead (1949) found *Staph. aureus* in the eyes of 19 of 35 infants with apparently normal conjunctivae. This suggests a lack of that protective mechanism present in adults. There appear to be no references to 'lysozyme' activity in the neonatal conjunctival sac; it seems likely that, in common with other active humoral defence systems, that of the conjunctiva is poorly developed at birth and becomes manifest after 2-3 months. This is the period about which Cunliffe (1949) observed a dramatic fall in the nasal carriage rate for *Staph. aureus*.

Sensitivity and Phage Reaction in Staph. aureus from Infections

There was a close correspondance in sensitivity and 'phage reaction between strains isolated from infant infections, both "pustules" and "sticky-eyes", and from the Infant Routine Swabs. Only 4 strains of *Staph. aureus* were sensitive to all antibiotics. There was an overwhelming preponderance of 'phage Group 3 and a very low incidence of Groups 1 and 2 and of untypable strains.

The frequency of Similar Types from Different Sources in Infant and Mother

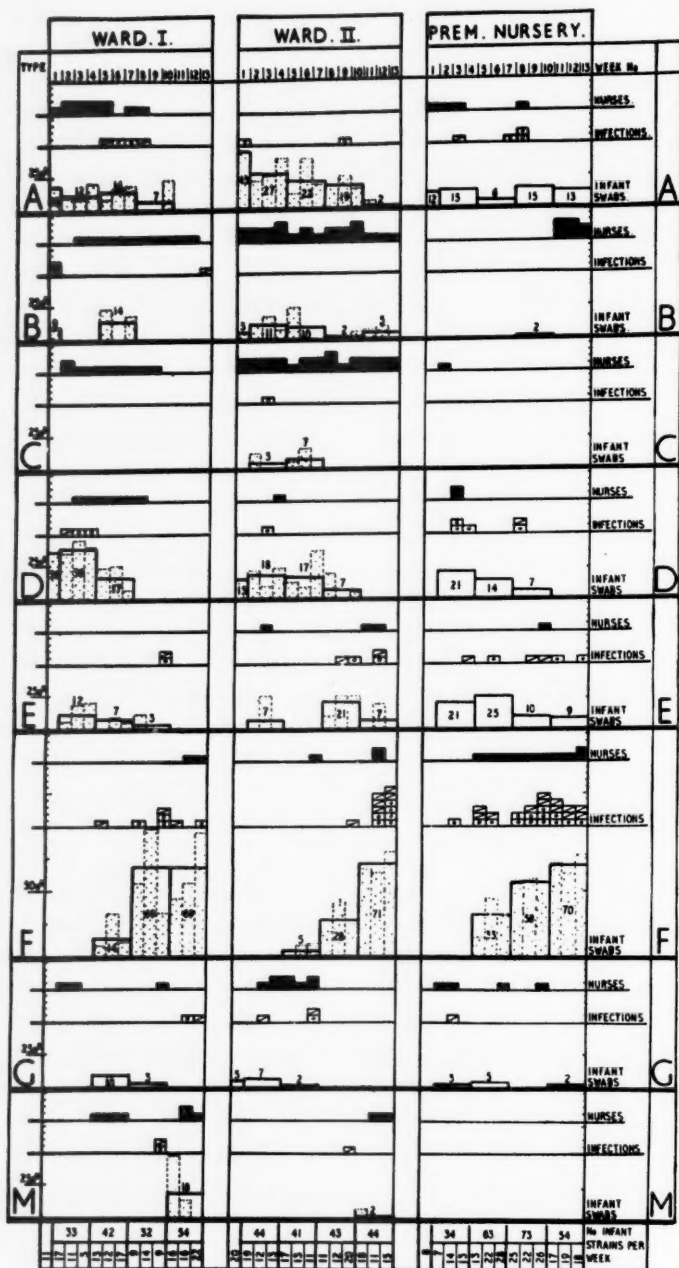
Of 54 cases the same 'phage type was isolated from the baby's pustule and nose in 74 %: from the pustule and umbilicus in 72 %, and from all three sites in 44 %.

Of 51 cases the same type was isolated from the "sticky-eye" and nose in 59 %: from the eye and umbilicus in 41 % and from all 3 sites in 29 %.

The correlation between pustule, nose and umbilicus was significantly higher than between the "sticky-eye", nose and umbilicus. This lends weight to the view that "sticky-eyes" were secondary infections and that any organism or strain of *Staph. aureus* present in the air or dust might have found lodgement in the eye at random.

In a total of 34 cases the mothers' nasal swab taken at the time of infection yielded the same 'phage type as 32 % of infants' pustules, 35 % of infant nares, 29 % of umbilical swabs, and 18 % were similar at all 4 sites. Likewise of 33 cases, the mothers' nasal strain proved similar in 24 % of "sticky-eyes", 27 % of infant nares, a 33 % of umbilical swabs, and 12 % were similar at all 4 sites.

Only one instance of infant sepsis with the mother's admission strain was proven. The occurrence of 5 other 'phage Group 1 and 2 strains in



infections on Wards 1 and 2 and the complete absence of such strains in the Premature Nursery suggested that transfer might have taken place on several other occasions.

NURSING AND WARD STAFF

From 74 nurses, orderlies and ward maids 477 nasal swabs were obtained, 276 (57.9 %) were positive for *Staph. aureus*. The salient points of nasal carriage in the staff of Wards 1 and 2 and the Premature Nursery are set out in the histogram (Fig. 1); as the Labour Ward staff are not included in Fig. 1, the following summary is given. Of 132 swabs, 40 (30.4 %) yielded *Staph. aureus*. Six nurses of the permanent Labour Ward staff were consistently negative for *Staph. aureus*. Polyantibiotic resistant 'phage Group 3 strains were found only 9 times in 6 persons who were all temporary carriers. It was possible on one occasion only, to relate nasal carriage to that of an infant.

In this case a nurse carried type M from the 5th to the 10th week of the study. She was on duty in Ward 1 for the first 3 of these weeks and on night duty in the Labour Ward for the last 3 weeks. One infant whom she delivered and 2 at whose delivery she assisted, developed infection associated with her strain of organism. At the same time 3 mothers acquired type M and it appeared in the ward dust for the first time. Subsequently the organism spread to another mother, a baby and 4 other nurses (see Fig. 1). It is of interest that spread through the hospital to dust and other nurses occurred promptly after the first infants were infected. The sequence is similar to that cited by Rountree & Barbour (1950).

Table 5 summarizes the 'phage reactions of the ward staff strains. Groups 1 and 3 had the same frequency of 31.3 %, Group 2 was very infrequent and has been omitted; the remaining strains were untypable at R.T.D. A much closer relationship is apparent between the 'phage types carried by mothers on discharge and their babies than between those of nurses and infants. Both discharge-mothers and babies had high carriage rate of Group 3 and a low rate of Group 1 despite maternal carriage of Group 1 on admission being 28.8 % of carriers. In the Premature Nursery, where no mothers were present, infant carriage of Group 1 was only 2.6 % of

Fig. 1. The incidence of 8 'phage types of *Staph. aureus* over a 13-week period, isolated from infants' routine nasal and umbilical swabs, infants' infections and nurses' nasal swabs on 3 wards.

Nurses' nasal carriage expressed in absolute numbers of carriers per week per ward.

Infections: □, pustules; ▣, sticky-eyes. Expressed in absolute numbers per week per ward.

Infant carriage expressed as a percentage of strains isolated over 3-week periods. Stippled areas represent the percentage of strains isolated in any week where this was of especial interest or the deviation from the 3 week mean large. The number of strains upon which each percentage is based appears at the base of the diagram.

TABLE 5

Comparison of distribution of Group 1 and 3 strains of Staph. aureus in nurses, infants and mothers.

	% of strains grouped according to phage Type		Total strains
	1	3	
Ward 1 & 2 mothers, admission (a)	28.8	10.6	170
Ward 1 & 2 mothers, discharge (b)	11.4	54.2	201
Infants (c)	8.4	81.0	596
Nurses (d)	31.3	31.3	276

TABLE 6

Comparison of antibiotic resistance of strains of Staph. aureus from nurses and mothers on discharge and from infant routine swabs.

	Nurses		Mothers on discharge		Infant routine swabs	
	No.	%	No.	%	No.	%
Completely sensitive	24	8.7	80	39.6	53	8.9
Penicillin-resistant	252	91.3	121	60.4	545	91.1
Streptomycin-resistant	59	21.4	83	41.3	437	73.3
Chloromycetin-resistant	10	3.6	14	7.0	127	21.3
Terramycin-resistant	4	1.4	8	4.0	97	16.3
Total	276		201		596	

strains compared with 12.4 % in babies on the other wards (Table 4) despite the fact that there the carriage of Group 1 was higher (43 %) than in the nurses as a whole (31.3 %). In the last 3 weeks of the study, when infant carriage of Group 3 strain "F" was reaching a peak (Fig. 1), Group 1 strains accounted for 70.7 % of all *Staph. aureus* isolated from nurses' noses. Furthermore there was a complete absence of phage type A on Ward 2 amongst nurses (Fig. 1) yet infant carriage was considerable. Again strain "F" was

found in infants on the wards several weeks before it was demonstrated in the nose of any nurse. The conclusion was inescapable that infant carriage preceeded and was little influenced by nurses nasal carriage. Nurses nasal strains were in the long run a reflection of strains carried by infants: a similar conclusion to that reached by Rountree & Thomson (1952).

Table 6 shows that comparison of strains isolated from different classes of person within hospital, on the basis of sensitivity to a single antibiotic can lead to false conclusions. With the exception of penicillin, the sensitivity of strains from mothers and babies bear a greater similarity to each other than do those from nurses and infants. The differences between nurse and maternal strains become more striking when the time at risk of each is considered. Here the findings support those of Forfar and his co-workers (1953). However, the close similarity of penicillin-resistance figures in infants and nurses, 91 % in each case, are consistent with those found by Barber, Hayhoe & Whitehead, 1949, and by Barber, Wilson, Rippon & Williams, 1953. The discrepancy may possibly be explained as follows. In the present study penicillin-resistant strains from nurses comprised both 'phage Groups 1 and 3 whereas those from babies were almost entirely Group 3. In the studies of Barber and her colleagues Group 1 strains appear to have been stable in the hospital(s) examined. These strains rarely become resistant to antibiotics other than penicillin. Since 52A is a common type in the general population (as in the present study amongst nurses), the appearance of similarity between infant and nurse strains does not necessarily imply that the strains represent a single distinct population, characterised by 52A and penicillin-resistance, or have a common source. It may be only that the infants happened to cultivate a common type and that the tools at our disposal are incapable of further definition of staphylococcal populations within this common type.

MEDICAL STAFF, STUDENTS AND PHYSIOTHERAPISTS

Of a total of 253 swabs from medical staff, students and physiotherapists 95 strains of *Staph. aureus* were isolated. Nasal carriage in this group of persons was considered to be of no significance in the study.

DUST

The dust sampled in the last 6 weeks of the study contained between c. 10,000 and 150,000 *Staph. aureus* per gram. All 'phage types found in lesions in babies were isolated on at least one occasion. Of 68 strains, 70.6 % were Group 3, 5.9 % Group 1 and 23.5 % were untypable at R.T.D. The predominance of Group 3 over Group 1 strains suggested that contamina-

tion of hospital environment occurred to an insignificant degree as a result of adult nasal carriage. The close similarity of the dust strains to those carried by babies suggested that the latter were the main source of organisms in the hospital. The sequence of events in the case of the type M strain confirmed this view, which was also the contention of Melin & Wallmark (1949).

The Position of the More Common Types in the Hospital Environment

Figure 1 gives the incidence of some of the more common types found in Infant Routine Swabs, in pustules and sticky-eyes and in nasal swabs from the ward nursing staff.

Of interest was the high incidence of type A on Ward 2 during the early part of the study and its extinction at the end. The reverse picture was shown by type F, which appeared in a pustule in the 3rd week in the Premature Nursery and which by the 13th week accounted for 95 % of strains carried by babies on Ward 1, for 80 % on Ward 2 and for 78 % in the Premature Nursery.

Infant colonization by some strains varied widely from ward to ward. Type B was frequently present on Ward 2, almost completely absent from the Premature Nursery and appeared sporadically on Ward 1. Type D accounted for 36 % of strains from infants on Ward 1 in the 1st week and was not found in the Nursery at this time. Carriage of type C was confined to infants on Ward 2 and type M to infants on Wards 1 and 2.

The occurrence of a high colonization rate in infants in the absence of nasal carriage amongst nurses was seen on a number of occasions. Examples: type A, Ward 2, and type F, Ward 1 (no isolations from nurses until 11th week in spite of all strains from infants being of type F in the 8th week). On the whole the incidence of infection with any particular strain ran parallel to its carriage rate in Infant Routine swabs, but sometimes a high carriage rate occurred silently without infection (type A, Ward 2, weeks 2-8).

It appears generally assumed that only limited variations in the incidence of any strain occur over relatively long periods of time. Stippled areas in Fig. 1 show that considerable changes may take place in as little as a week. Such changes would affect the validity of conclusions based on infrequent sampling of different sections of a hospital population. For example, had infants been swabbed on Ward 2 in week 5 only, type B (24 % of strains) would have appeared to be of more general frequency than other strains: however, in both weeks 4 and 6, type A had an incidence of 39 % of strains. A rapid turnover of a very susceptible infant population is thought to be the cause of these variations.

The rise in incidence of type F coincident with a fall in that type A implies some property of the organism distinct from an ability to cause disease. Parker & Kennedy (1949) used the term "transmissability" which indicates passive selective transfers, on hands etc., of one type rather than another. The chance of passive transfer for two strains should be in proportion to their prevalence at the time, it is difficult to explain our observations on this basis. A hypothesis based on differential generation times, due either to altering environmental or internal bacterial factors, fits better with the observed facts.

A distinction may possibly be drawn between the ability to multiply and the ability to cause disease however trivial, if this does not ultimately depend upon minute lesions of the infant cutis as has been suggested by Maguire (1903) and Knott & Blaikley (1944). If infant pustules depend on such cutical lesions then the extent to which pustules occur will depend not only on these but on the prevalence of the organism on the infant surface and the severity of any resulting disease on an intrinsic property of the infecting germ (? pathogenicity). Whether septic lesions are "open" or remain "closed" will affect the numerical ward population, but in the absence of "open" staphylococcal lesions the organism must rely on extensive infant colonisation (moist surfaces, umbilical stump, faeces etc.) to produce its numbers. The coccus with the shorter generation time will gain supremacy. Thus a strain of low incidence may cause sporadic cases of severe "closed" disease (cf. Allison & Hobbs, 1947) and one of high incidence but low pathogenicity (i.e. type F) a large number of minor lesions: if suitable portals of entry are unavailable, then a high "silent" carriage rate may result.

Detail of type F

Type F arose apparently *de novo* during and achieved the status of a potentially epidemic strain by the end of the study. It was first isolated from a vesicular lesion in a baby's scalp in the Premature Nursery in the 3rd week; it was also present in the nose and umbilicus of this baby at the time of infection (these are not shown in Fig. 1 since they were not "routine" swabs). In the 4th week it was not isolated from any source, but dust was not being examined at this time. In the 5th week it was isolated from a night nurse, who carried an unrelated strain in the 3rd week; from three infections in the Nursery and one on Ward 1 and from routine infant swabs from both wards and Nursery. Later the frequency of isolation of type F increased until most of the strains from infants, infections and from dust were of this type. It was also found in a large number of mothers on discharge but did not commonly appear in nurse's nasal swabs and was never isolated from the Labour Ward staff.

The Persistence of "Hospital Strains" of *Staph. aureus* in Mothers after Discharge from Hospital

Twenty-eight women who were discharged from hospital carrying easily identifiable strains of *Staph. aureus* were examined for persistence of carriage. Eighteen women were seen at the post-natal clinic, 6 weeks after discharge: 7 (39 %) were carrying hospital strains. One was carrying not her own discharge strain but that of her infant: 2 were carrying strains different from both mother and infant discharge types. Five were no longer carriers and 7 carried non-hospital types.

Ten women were visited at home 6 months after discharge. Two mothers were still carrying type F, but their infants were negative. One infant whose mother had become negative still carried type F.

Two interesting families were found. In one, the mother continued to carry type F, resistant to penicillin and streptomycin, the infant's two older sisters also carried type F but one strain was resistant to penicillin only and the other sensitive to all antibiotics. It is very likely that both sisters derived their nasal strains from the mother, her baby from clothing etc. contaminated in hospital: type F has a general population incidence of $< \frac{1}{100}$, the probability of isolating it by chance on 3 successive occasions is less than 1 in 1,000,000. If this surmise is correct, the findings provide reasonable evidence that when removed from the hospital environment, resistant strains may revert to sensitivity.

The second interesting family was a large one living in cramped quarters. A type 42E strain of *Staph. aureus* was isolated from the nose of the infant, mother, grandmother and 2 aunts, it was absent from the grandfather and 3 uncles. Carriage of the same strain by female members only may have been a reflection of their more intimate contact with the baby.

The question of the persistence of "hospital" antibiotic-resistant organisms in the population at large following discharge from or even visits to hospital is of the first importance. Further work is clearly required to assess the extent to which *Staph. aureus* is carried to the home and spread around the mother's and infant's associates. However, in this study although about 40 % of potentially infected homes existed at the time of discharge from the mother's nose alone, the relative infrequency of resistant strains from admission swabs and the continued clinical usefulness of penicillin in *Staph. aureus* infections, unconnected with hospital practice, indicates that up to the present, resistance levels in the general population have risen only to a minor degree.

Acknowledgements

We acknowledge with gratitude the co-operation of all medical and nursing staff in the hospital studied.

Thanks are due to the Late Professor Sir James Spence and members of the staff of the Department of Child Health, to Professor H. Harvey Evers and staff of the Department of Midwifery and Gynaecology, to Dr. C. A. Green of the Department of Bacteriology, Royal Victoria Infirmary, for laboratory facilities and much valuable advice, and to Dr. R. E. O. Williams and Miss Joan E. Rippon of the Staphylococcal Reference Laboratory, Colindale, for teaching one of us (J.G.P.H.) the technique of phage typing and for checking a number of staphylococcal strains.

Summary and Conclusions

Staphylococcal epidemiology in its relation to infant infection was studied intensively over a 13-week period in a maternity hospital.

From 3542 swabs from infants, mothers, hospital staff and dust 2260 strains of *Staph. aureus* were isolated.

The bacteriology of 64 pustules and 93 sticky-eyes was studied. Infections were all minor, the majority running a self-limited course of a few days.

The following conclusions were drawn from the evidence obtained:—

1. Mothers with infants at the bedside acquired hospital strains of *Staph. aureus* more frequently and more rapidly than did nurses in a nursery environment or prospective mothers in a ward without babies.

2. Although both nurses and mothers might transmit their nasal strains of *Staph. aureus* to infants, this was an infrequent occurrence and of little importance in the total spread of an organism in the hospital.

3. Colonisation of the infant nose and umbilical stump by *Staph. aureus* was extremely rapid (66.8 % at one or other site within 24 hours of birth).

4. Infant colonisation and disease resulted largely from cross infection infant to infant.

5. Nursery conditions predisposed to a higher incidence of neonatal infection than occurred if the infant was cared for at the mothers bedside in a lying-in ward.

6. The majority of skin pustules were of staphylococcal aetiology even though pin-point in size. Some at least of the sticky-eyes were not bacterial infections; a chemical or viral aetiology could not be excluded.

7. The contamination of dust with *Staph. aureus* was due almost entirely to dissemination from infants who acted as the culture medium.

8. The picture of the hospital staphylococcal environment was of waves of one or more major strains waxing and waning over a period of weeks or months with undercurrents of minor types occurring sporadically or at low levels, the whole system in a state of flux and liable to sudden variation without warning.

9. Both mothers and infants frequently carried home hospital strains of staphylococci. Some of these persisted for at least 6 months and spread within the family group occurred.

Epidémiologie staphylococcique dans une maternité.

L'épidémiologie staphylococcique, dans sa relation avec l'infection de l'enfant, a été l'objet d'une étude approfondie poursuivie pendant 13 semaines dans une maternité. Il a été isolé 2260 souches de staphylocoques dorés de 3542 prélèvements faits chez des enfants, des mères, du personnel et des poussières. 64 pustules et 93 yeux en état d'inflammation ont été étudiés bactériologiquement. Les infections étaient toutes légères se bornant le plus souvent à une indisposition guérissant généralement d'elle-même en peu de jours.

Staphylokokken-Epidemiologie in einer Entbindungsanstalt.

In einer Entbindungsanstalt wurde die Staphylokokken-Epidemiologie in ihrem Verhältnis zur Säuglingsinfektion in einem Zeitraum von 13 Wochen eingehend untersucht. Aus 3542 Abstrichen bei Säuglingen, Müttern, Krankenhauspersonal und Staub wurden 2260 Stämme von *Staph. aureus* isoliert. Ferner wurde die Bakteriologie von 64 Pusteln sowie 93 Fällen von Blepharitis ciliaris untersucht. Die Infektionen waren alle von geringer Bedeutung; der grösste Teil begrenzte sich auf den Verlauf von einigen Tagen.

Epidemiología estafilocócica en una maternidad hospitalicia.

La epidemiología estafilocócica y su relación con la infección de los lactantes fué estudiada intensivamente durante un período de 13 semanas en una maternidad hospitalicia. Se aislaron 2260 cepas de *Staph. aureus* partiendo de 3542 tapones de algodón provenientes de lactantes, madres, personal hospitalero y polvo. Se estudió la bacteriología de 64 pústulas y 93 ojos pringosos. Todas las infecciones fueron leves, la mayoría siguiendo un curso propio limitado a unos cuantos días.

Appendix

*Index of 'phage and usual sensitivity reactions of the commoner types of Staph. aureus.**Code letter*

- A 42E/6/7/47/53/54/73/75/42C/47B/47C. Invariably resistant to penicillin and streptomycin, often to chloromycetin, rarely to terramycin.
- B 52A. Penicillin-sensitive or resistant; resistance to other antibiotics rare.
- C+ 29/44/52A/6/7/47/54/70/73/75. Invariably resistant to penicillin and sensitive to other antibiotics.
- D 53/75/76/77. Invariably resistant to penicillin and streptomycin, resistance to other antibiotics variable.
- E 7/47/53/54/75/76/77. Usually resistant to penicillin and streptomycin, resistance variable to other antibiotics.
- F 75A. Invariably penicillin- and streptomycin-resistant, resistance to chloromycetin and/or terramycin frequent.
- G 75/76/77W. Usually resistant to penicillin and streptomycin, sometimes to other antibiotics.
- M+ 29/44/7. Invariably resistant to penicillin only.
+ Typable with undiluted filtrates only.

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Chronic Idiopathic Autoimmune Hemolytic Disease in Childhood

by ANDERS LARSON

Autoimmunization as a cause of acquired hemolytic disease was recognized about ten years ago with the introduction of new serologic techniques.

The basic pathologic feature in this disorder is the appearance of abnormal auto-antibodies in the patient's blood which are capable of acting on his own red cells. This leads, by some not yet fully explained mechanism, to a shortening of the life span of the red cells. Unless the bone marrow fails to provide an adequate replacement, anemia develops. The cause of the autoimmunization remains obscure. Reviews of the pertinent literature have been published by Dacie (1955) and Dameshek (1955).

Chronic autoimmune hemolytic anemia is found in all age groups, though most reports deal with its occurrence in adults. In childhood the acute type is dominating, while the chronic form seems to be rare (cf. Gasser, 1951; Verger, Moulinier, Martin and Danan, 1954). In this report the clinical features in two patients with the chronic variety will be described. Despite treatment with Corticotropic hormone and blood transfusions the disease terminated fatally in one of the patients. In the second child the disease ran a benign course after the institution of hormone treatment, and the patient went into a partial remission.

Case Reports

Case 1

E. J., a 13-month-old girl, was admitted to this Clinic on February 21, 1955.

History.—She was the eighth child of healthy parents. There was no family history of hemolytic disease, and no personal history of previous illness. Birth weight was 3700 g. She had been admitted to the local hospital on January 20th, with a history of gradually increasing pallor, fretfulness, and anorexia for the past ten weeks. Two days before admission her condition had become worse, with slight fever, vomiting and rapidly increasing pallor. Examination had shown a very ill, extremely pale child, with slight jaundice, and moderate enlargement of the liver and spleen. Blood examination showed Hb. 17 %, red cells 790,000 per cmm. After repeated blood transfusions the hemoglobin level had risen to 87 %. The hemolytic process had, however, persisted, the reticulocyte count varied between 5 and 8 %, and two relapses occurred.

Physical examination on admission revealed a normally developed, moderately ill child with pronounced pallor. The liver was felt 3 cm below the costal margin and the spleen 5 cm below the costal margin. There was no enlargement of the lymph nodes and no signs of hemorrhagic disorder.

Laboratory investigations.—Blood: Hb. 5.5 g %; red cells 1,400,000 per cmm, mean cell diameter 6.9μ (Price-Jones' curves); white cells 3100 per cmm; differential count, normal; thrombocytes 166,000; reticulocytes 27 %; considerable anisocytosis and polychromasia. The resistance of the red cells to hypotonic saline was normal. Serum bilirubin 1.76 mg per 100 ml. Bone marrow smear: erythroblastic hyperplasia; no other abnormalities.

*Serologic tests.*¹—Blood type B Rh positive, type CDe/CDe (Fischer's terminology). The direct Coombs' test was positive in a dilution of 1 in 512, with a zone phenomenon. The indirect test displayed a nonspecific autoantibody in the serum, and a common cold agglutinin in saline solution at low titer. The abnormal antibody was of the warm type. According to Dacie (1953) this is the usual finding in the majority of cases of acquired hemolytic anemia. No specificity for any special blood group antigen could be demonstrated.

Treatment and course.—The child was treated with ACTH and blood transfusions. The principal hematologic data during treatment are shown in Fig. 1.

Despite the treatment the high intensity of the hemolytic process persisted and re-

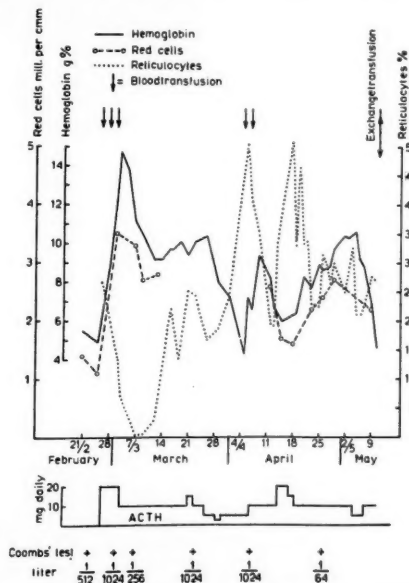


Fig. 1. Case 1. The principal hematologic data during the course. Note the tendency to relapses and the ineffectiveness of blood transfusions. As indicated by the high reticulocyte count the intensity of the hemolytic process persisted despite hormone treatment.

¹ The serologic tests have been performed at the State Rh-Laboratory. I am indebted to Dr. B. Broman and Dr. B. Löw for performing these tests.

lapses occurred. The liver and spleen remained unchanged in size. After the first 4 week period of ACTH therapy she gained 1.2 kg in weight, and a marked rounding of the face was noted.

Two months after admission there were signs of clinical improvement, with marked decrease in the size of the liver and spleen, and an increase in the hemoglobin level. The direct Coombs' test was still positive in a dilution of 1 in 64. The indirect test showed only a weak antibody. The high reticulocyte count showed, however, that the hemolytic process was still very active.

A reduction in the ACTH to 5 mg per day was accompanied by a rapid fall in the hemoglobin level, and an upper respiratory tract infection developed. Within a few days the hemoglobin level had fallen to 4.6 g %. Her general condition deteriorated rapidly, and consciousness was almost lost. In order to reduce the amount of antibody and because of the resistance of the hemolytic process to ACTH therapy, an exchange transfusion was performed, consisting of the administration in local anesthesia of 1450 ml of compatible whole blood and withdrawal of 1300 ml of venous blood. Because of an anomaly of the saphenous vein the transfusion was given in the iliac vein. No difficulties were encountered during this procedure. When the wound was to be sutured, however, the child became restless and a light general anesthesia (ether + N₂O) had to be given. The child then was in fairly good condition until about an hour after the transfusion was finished, when she went into a state of acute shock, and died without having regained consciousness. No serologic explanation of her death could be demonstrated. Permission for autopsy was refused.

Case 2

K. L., a 12-year-old girl, was admitted to this Clinic on September 12, 1955.

She was the second child of healthy parents. There was no known family history of hemolytic disease, and no personal history of previous illness. During the month prior to admission it was noticed that she became progressively paler and tired easily.

Physical examination showed a normally developed, very pale girl, with slight jaundice. Her weight was 37.5 kg. There was no enlargement of the liver or spleen, and no lymphadenopathy. There were no symptoms suggestive of infectious disease or hemorrhagic disorder.

Laboratory investigations.—*Blood:* Hb. 5.5 g %; red cells 1,500,000 per cmm, mean cell diameter 7.2 μ ; white cells 1900 per cmm (polymorphs 72.5 %, lymphocytes 27.5 %); thrombocytes 66,000 per cmm; reticulocytes 40.5 %; sedimentation rate 144 mm/hr. The blood smear showed considerable anisocytosis, polychromasia and basophilic stippling of the red cells, no spherocytosis. No L.E. cells could be demonstrated. The resistance of the red cells to hypotonic saline was normal. Serum bilirubin 2.8 mg per 100 ml. The electrophoretic pattern of the serum proteins was normal. Bone marrow smear: nonspecific erythroblastosis.

Serologic tests.—Blood type A₁ Rh positive, CDe/CDe. The direct Coombs' test was positive in a dilution of 1 in 512. The serum contained a nonspecific auto-antibody of the warm variety and a weak ordinary cold agglutinin.

Treatment and course.—The child was placed on ACTH and cortisone therapy. The main hematologic data and treatment are shown in Fig. 2.

One month after admission her hemoglobin was 10.3 g %, reticulocytes 11.6 %, white cell count 4900 per cmm, platelets 280,000 per cmm. (The low platelet and white cell counts on admission may have been due to an immunologic mechanism (cf. Evans and Duane, 1949)). There was a decrease in serum bilirubin to 0.6 mg per 100 ml. The

Den goda effekten hos
Tyzanol framgår av de
"utmärkta resultat"
som erhållits i nära
95 % av 1.058 publicerade
fall.¹⁻⁴ Tyzanol ger
omedelbar lindring,
som varar 4-6 timmar
efter första dosen.
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i näsan förekommer.
Preparatet är behagligt
att använda och
praktiskt taget smak-
och luktfritt.

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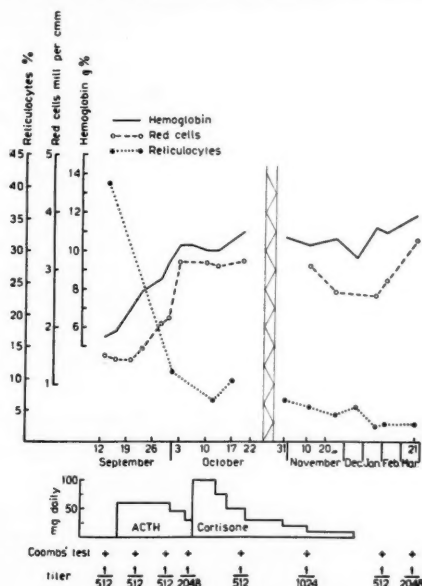


Fig. 2. Case 2. The main hematologic data during hospitalization and follow-up examinations. There is a good response to hormone therapy. The hemolytic process is brought under control.

direct Coombs' test was still positive, however, and the serum contained free auto-antibodies. The sedimentation rate returned to normal. Because of the development of a "moonface", and the fact that the hemoglobin level tended to be stabilized between 10 and 11 g %, the hormone therapy was successively decreased. Seven weeks after admission she was discharged, in good physical condition, on a maintenance dose of 30 mg of cortisone daily.

A follow-up examination six months after discharge showed that the hemolytic process was still active, but decreased in intensity. She had then been without hormone therapy for three months. Her hemoglobin was 12.4 g %, reticulocytes 2.6 %, white blood cells 3700 per cmm. The direct Coombs' test was positive in a dilution of 1 in 2048. Free antibodies were still present in the serum but the reactions were weaker than before.

When last seen nine months after discharge the girl was in good physical condition. Her hemoglobin concentration was 13.1 g % and reticulocytes 1.5 %.

Discussion

The two patients reported here exhibited the clinical features characteristic of chronic autoimmune hemolytic anemia. In neither of the children was there a history of exposure to viral disease or other infections, and as no other etiological factor could be demonstrated the condition must be considered "idiopathic".

The differentiation between autoimmune hemolytic anemia and other forms of hemolytic anemia, which is largely determined by serologic tests, can usually be done with accuracy if the patient is studied for a sufficient length of time (Young and Miller, 1953). As a rule, a negative Coombs' test excludes an immunologic mechanism. Assessment of the quantitative changes in antibody titer (quantitative Coombs' test) presents considerable difficulties, and reports on a relationship between the antibody titer and the activity of the disease are controversial (Evans and Duane, 1949; Young *et al.*, 1951; Gardner *et al.*, 1951; Sacks *et al.*, 1952). A favourable clinical response to treatment is not always accompanied by a corresponding reduction in antibody titer. The current view is that no definite correlation exists. In Case 1 in the present series there was a definite reduction in antibody titer during the phase of remission, while in Case 2 the titer remained unchanged or increased during remission. The Coombs' test may remain positive for years in patients without clinical signs of disease.

The treatment of autoimmune hemolytic anemia has been advanced considerably by the introduction of ACTH, cortisone and more recently prednisone. Their exact mode of action is not fully recognized, but in most cases these hormones have a controlling effect on the rate of destruction of the red cells, and may be given for months or even years without apparent toxic effects. During the time a complete or partial remission may be induced. If one of the hormones fails, the others should be tried and may be of benefit. The importance of adequate dosage has been stressed by several authors (Dameshek, 1952; Brit. Med. Research Council, 1955). However, after discontinuing therapy there is great tendency to relapse (Meyers *et al.*, 1952), and it may be necessary to perform splenectomy which was the mainstay in the treatment of hemolytic anemia up till 1950. It is impossible to predict the effect of hormone treatment or splenectomy in the individual case. The use of hormone therapy or splenectomy alone may be useful in many cases, but a combination of the two may be superior.

Reports on the results of hormone treatment in children are sparse. Meyer (1951) reported a lasting remission in a 13-month-old boy, who did not respond to transfusions, by giving ACTH in doses at times as much as 80 mg daily. Fontan *et al.* (1955) obtained a complete remission in a 5-month-old girl, and Verger *et al.* (1954) at the same clinic obtained good results in a 3½-year-old boy with chronic idiopathic autoimmune hemolytic anemia. Recently O'Connor *et al.* (1956) reported remissions to date of 5 years and 1 year, respectively, in two young children who had also undergone splenectomy. Stickney and Mills (1952), on the other hand, noted a temporary improvement in only one of three children treated. Rose and Nabarro (1953), who treated four children with acute hemolytic anemia with relatively large

doses, noted clinical toxic effects without evidence of electrolyte disturbances. Routine blood counts during the period of withdrawal of ACTH gave no warning of a relapse before a sudden fall in hemoglobin concentration necessitated a blood transfusion. In Case 1 a rapid fall in hemoglobin was also noted following a decrease in dosage.

Transfusions were only of temporary benefit in Case 1. They are often useful, however, in carrying a patient through crisis and may at times be life-saving. However, their use should be restricted because of the danger of sensitization to a group antigen in this disease. Concentrated red-cell suspensions or washed cells should be used in order to avoid a plasma transfusion reaction (Dameshek, 1950). Bowman (1955) has reported the successful use of exchange transfusion in a child in crisis, allowing time for the hormones to act. Its use in adults has been of little or no benefit. In Case 1 it proved of no effect and together with the anesthetic manipulations it might even have played some part in the deleterious outcome of the patient. Recently Roth *et al.* (1956) reported an immediate effect of heparin on antibody activity in a 15-year-old girl with autoimmune hemolytic anemia. Heparin is thought to become a useful adjunct in the initial treatment of the disease.

Reports on the prognosis in childhood are sparse. Millichap (1952), in a review of the literature from 1940-1950, found only 3 fatalities in 32 cases of acute idiopathic hemolytic anemia. In adults the prognosis was less favourable, but Dausset and Malinvaud (1954) reported a reduction in mortality of 20% in idiopathic cases since the advent of hormone therapy in 1950. The mortality is still about 30%. As far as the author is aware, nothing has been published on the prognosis of the chronic type in childhood. This may partly be due to the sparsity of follow-up studies of patients with complete remissions. It may be stated, however, that the use of ACTH, cortisone and prednisone has much improved the outlook, but at the same time it must be remembered that the effects of therapy in this disease are often difficult to assess because it runs an uncertain course of remissions and exacerbations with a tendency to spontaneous recovery. Consequently the final outcome in individual patients is still uncertain.

Summary

Two cases of chronic idiopathic autoimmune hemolytic anemia in childhood have been described. One of the patients died despite intensive treatment with ACTH, blood transfusions and an exchange transfusion. The second patient showed a good response to hormone therapy, the hemolytic process being brought under control. The Coombs' test has remained positive, but the patient has been without signs of anemia for 6 months after the withdrawal of therapy.

The differentiation between autoimmune hemolytic anemia and other forms of hemolytic anemia, which is largely determined by serologic tests, can usually be done with accuracy if the patient is studied for a sufficient length of time (Young and Miller, 1953). As a rule, a negative Coombs' test excludes an immunologic mechanism. Assessment of the quantitative changes in antibody titer (quantitative Coombs' test) presents considerable difficulties, and reports on a relationship between the antibody titer and the activity of the disease are controversial (Evans and Duane, 1949; Young *et al.*, 1951; Gardner *et al.*, 1951; Sacks *et al.*, 1952). A favourable clinical response to treatment is not always accompanied by a corresponding reduction in antibody titer. The current view is that no definite correlation exists. In Case 1 in the present series there was a definite reduction in antibody titer during the phase of remission, while in Case 2 the titer remained unchanged or increased during remission. The Coombs' test may remain positive for years in patients without clinical signs of disease.

The treatment of autoimmune hemolytic anemia has been advanced considerably by the introduction of ACTH, cortisone and more recently prednisone. Their exact mode of action is not fully recognized, but in most cases these hormones have a controlling effect on the rate of destruction of the red cells, and may be given for months or even years without apparent toxic effects. During the time a complete or partial remission may be induced. If one of the hormones fails, the others should be tried and may be of benefit. The importance of adequate dosage has been stressed by several authors (Dameshek, 1952; Brit. Med. Research Council, 1955). However, after discontinuing therapy there is great tendency to relapse (Meyers *et al.*, 1952), and it may be necessary to perform splenectomy which was the mainstay in the treatment of hemolytic anemia up till 1950. It is impossible to predict the effect of hormone treatment or splenectomy in the individual case. The use of hormone therapy or splenectomy alone may be useful in many cases, but a combination of the two may be superior.

Reports on the results of hormone treatment in children are sparse. Meyer (1951) reported a lasting remission in a 13-month-old boy, who did not respond to transfusions, by giving ACTH in doses at times as much as 80 mg daily. Fontan *et al.* (1955) obtained a complete remission in a 5-month-old girl, and Verger *et al.* (1954) at the same clinic obtained good results in a 3½-year-old boy with chronic idiopathic autoimmune hemolytic anemia. Recently O'Connor *et al.* (1956) reported remissions to date of 5 years and 1 year, respectively, in two young children who had also undergone splenectomy. Stickney and Mills (1952), on the other hand, noted a temporary improvement in only one of three children treated. Rose and Nabarro (1953), who treated four children with acute hemolytic anemia with relatively large

doses, noted clinical toxic effects without evidence of electrolyte disturbances. Routine blood counts during the period of withdrawal of ACTH gave no warning of a relapse before a sudden fall in hemoglobin concentration necessitated a blood transfusion. In Case 1 a rapid fall in hemoglobin was also noted following a decrease in dosage.

Transfusions were only of temporary benefit in Case 1. They are often useful, however, in carrying a patient through crisis and may at times be life-saving. However, their use should be restricted because of the danger of sensitization to a group antigen in this disease. Concentrated red-cell suspensions or washed cells should be used in order to avoid a plasma transfusion reaction (Dameshek, 1950). Bowman (1955) has reported the successful use of exchange transfusion in a child in crisis, allowing time for the hormones to act. Its use in adults has been of little or no benefit. In Case 1 it proved of no effect and together with the anesthetic manipulations it might even have played some part in the deleterious outcome of the patient. Recently Roth *et al.* (1956) reported an immediate effect of heparin on antibody activity in a 15-year-old girl with autoimmune hemolytic anemia. Heparin is thought to become a useful adjunct in the initial treatment of the disease.

Reports on the prognosis in childhood are sparse. Millichap (1952), in a review of the literature from 1940-1950, found only 3 fatalities in 32 cases of acute idiopathic hemolytic anemia. In adults the prognosis was less favourable, but Dausset and Malinvaud (1954) reported a reduction in mortality of 20% in idiopathic cases since the advent of hormone therapy in 1950. The mortality is still about 30%. As far as the author is aware, nothing has been published on the prognosis of the chronic type in childhood. This may partly be due to the sparsity of follow-up studies of patients with complete remissions. It may be stated, however, that the use of ACTH, cortisone and prednisone has much improved the outlook, but at the same time it must be remembered that the effects of therapy in this disease are often difficult to assess because it runs an uncertain course of remissions and exacerbations with a tendency to spontaneous recovery. Consequently the final outcome in individual patients is still uncertain.

Summary

Two cases of chronic idiopathic autoimmune hemolytic anemia in childhood have been described. One of the patients died despite intensive treatment with ACTH, blood transfusions and an exchange transfusion. The second patient showed a good response to hormone therapy, the hemolytic process being brought under control. The Coombs' test has remained positive, but the patient has been without signs of anemia for 6 months after the withdrawal of therapy.

Maladie idiopathique autoimmune hémolytique chronique de l'enfance.

Description de 2 cas d'anémie chronique idiopathique autoimmune hémolytique concernant des enfants. L'un des malades est mort malgré un traitement intense par ACTH, des transfusions sanguines et une exsanguino-transfusion. Le second a bien réagi à la thérapie hormonale, ce qu'a montré le contrôle du procès hémolytique. Le test de Coombs est resté positif, mais l'enfant ne présentait plus de signes d'anémie 6 mois après que la thérapie eut cessé.

Chronische idiopathische autoimmune hämolytische Krankheit bei Kindern.

Es werden zwei Fälle von chronischer idiopathischer autoimmuner hämolytischer Anämie in der Kindheit beschrieben. Einer der Patienten starb trotz intensiver Behandlung mit ACTH, Bluttransfusionen und einer Exsanguino-Transfusion. Bei dem zweiten Patient konnte, nachdem der hämolytische Prozess unter Kontrolle gebracht war, eine günstige Reaktion auf Hormontherapie beobachtet werden. Die Coombsche Reaktion ist positiv geblieben, aber der Patient war nach Beendigung der Therapie während 6 Monate frei von Anämie.

Enfermedad hemolítica autoinmune idiopática crónica infantil.

Se describen dos casos de anemia hemolítica autoinmune idiopática crónica infantil. Uno de los pacientes falleció a pesar de un tratamiento intensivo con ACTH, transfusiones de sangre y una transfusión recíproca. El segundo paciente respondió satisfactoriamente a la terapéutica hormonal, lográndose restringir el proceso hemolítico. La prueba de Coombs permanece positiva, pero el paciente ha estado exento de signos de anemia durante 6 meses después de haberse cesado la terapéutica.

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Gallengangsmissbildung und Rhesus-Inkompatibilität

von PETER PAUL

Daß es im Verlauf eines Morbus haemolyticus neonatorum (M.h.n.) zur Verstopfung der kleinen intrahepatischen Ausführungsgänge durch Gallenthromben kommen und dadurch das Bild eines Okklusionsikterus entstehen kann, ist bekannt und wiederholt durch die Untersuchung exzidierten Lebergewebes belegt worden. Für die mutmaßlichen Ursachen der Obstruktion von Gallenkapillaren beim M.h.n. gibt es verschiedene Erklärungen, die aber über das Stadium der Hypothese kaum hinausgelangt sind.

So fehlt der Annahme einer Schädigung der Kapillarwand durch den direkten Zustrom des mit Antikörpern beladenen Nabelschnurblutes u. W. bisher der histologische Nachweis solcher Veränderungen. Von anderer Seite wurde eine Viskositätssteigerung der Lebergalle infolge der exkretorischen Funktionsschwäche des Organs bzw. eine Überbeanspruchung der noch unreifen Säuglingsleber durch die gesteigerte Erythropoese für das Geschehen verantwortlich gemacht. An die Möglichkeit einer Abflußbehinderung der Galle durch Schwellung des geschädigten Leberparenchyms wurde in diesem Zusammenhang auch gedacht (Zollinger, Craig, Hsia u. M., Lightwood u. Bodian).

Wie immer man die kausalen Vorgänge zu klären versucht, so bleibt doch auffällig, daß es keineswegs nur die besonders schweren Fälle von M.h.n. sind, die zum Obstruktionsikterus führen. Gar nicht so selten wird diese Komplikation als erste klinische Manifestation einer zuvor unerkannt gebliebenen hämatogenen Inkompatibilität gesehen, was zu dem Schluß geführt hat, daß sie bevorzugt in solchen Fällen auftritt, bei denen keine Austauschtransfusion durchgeführt wurde (van Creveld). Dabei entwickeln sich die charakteristischen Symptome nur bei einem Teil der Erkrankten in den allerersten Lebenswochen und gleichsam aus einem mehr oder weniger intensiven Neugeborenenikterus heraus, während sie bei anderen erst nach vorübergehendem Abklingen der postnatalen Gelbsucht und einem erscheinungsfreien Intervall von mehreren Wochen Dauer als erneut auftretender Ikterus mit Okklusionsbefunden im Stuhl, Urin und Blut einsetzen. Auch der weitere Ablauf der obstruktiven Phase des M.h.n. ist recht unter-

schiedlich. In der Mehrzahl der Fälle spielt sich der Gallenabfluß im Verlauf des zweiten Trimenons allmählich ein, der Ikterus verschwindet, die Stühle färben sich wieder, der Serumbilirubinwert normalisiert sich und Urobilino-gen wird nachweisbar. Bei einem kleineren Teil der betroffenen Säuglinge bleiben und verstärken sich hingegen die klinischen Erscheinungen, um schließlich in eine biliäre Cirrhose mit ungünstiger Prognose überzugehen (Gasser, Ewerbeck). Daneben gibt es natürlich auch Zwischenformen, bei denen es z. B. zu rezidivierenden Störungen mit temporären Verschlußsymptomen kommen kann.

Nachdem das klinische Bild des intrahepatischen Obstruktionsikterus beim M.h.n. das eines extrahepatischen Verschlusses durch eine Mißbildung der großen Gallengänge bzw. einen Stein oder Tumor täuschend kopieren kann, gewinnt die Differentialdiagnose im Hinblick auf die einzuschlagenden Behandlungsmaßnahmen größte Bedeutung (Opitz). Erschwerend kommt hinzu, daß beim jungen Säugling auch eine epidemische Hepatitis (Weisse, Stoppelman, Craig u. M., Gellis u. M.), ein konstitutioneller familiärer hämolytischer Ikterus und die seltene, kongenitale, nicht hämolytische Gelbsucht (Crigler u. M., Stransky) die gleichen intrahepatischen Verschlußsymptome zeigen können. Die zur Differenzierung herangezogene Bestimmung der alkalischen Serumphosphatase, die gebräuchlichen Leberfunktionsprüfungen, der Cholesterinwert u. a. erbringen leider in praxi nicht immer die erhofften eindeutigen Befunde, sondern lassen oftmals im Stich, worauf wiederholt von verschiedenen Autoren hingewiesen wurde. Auch die zur Klärung der Frage einer Inkompatibilität durchgeführten Blutuntersuchungen schließen bei positivem Ausfall eine zusätzliche Fehlbildung der Gallenwege im Sinne einer Atresie oder Agenesie keineswegs aus, wie unsere weiter unten beschriebenen Fälle zeigen werden.

Bei Bestehenbleiben des entsprechenden Zustandsbildes wird man somit schließlich einmal vor die Entscheidung gestellt, ob man noch länger zuwarten darf oder eine Probelaaparotomie vornehmen muß. Dabei wird der Zeitpunkt für ein chirurgisches Vorgehen nicht zu spät gewählt werden dürfen, weil ein Abwarten über den 4. und 5. Lebensmonat hinaus die Gefahr eines irreparablen Leberschadens in sich birgt. Daß bei ausschließlich intrahepatischen Veränderungen der operative Eingriff erfolglos beendet werden muß, ist eine der bei der vorliegenden äußerst schwierigen Differentialdiagnose unvermeidlichen Enttäuschungen, über die in der Literatur mehrfach berichtet wird.

So haben Harris u. M. 49 Kinder mit eindeutigen Verschlußsymptomen laparotomiert und in keinem einzigen Falle ein außerhalb der Leber liegendes Hindernis nachweisen können. Sechzehn ihrer Patienten hatten einen M.h.n. auf Grund einer Rhesus- oder ABO-Unverträglichkeit. Craig u. M. fanden bei 13 wegen Verdachts auf

Gallengangsatresie operierten Säuglingen keinen entsprechenden Befund. Es handelte sich ausnahmslos um frühkindliche Fälle einer epidemischen Hepatitis. Ähnliche Erfahrungen machten Kiesewetter u. M., sowie Hsia u. M. bei einem zahlenmäßig großen Krankengut junger Säuglinge. Sie fanden bei etwa 40 % der Laparotomierten hepatozelluläre Ikterusformen ohne operables Substrat; 15 % der Gesamtzahl hatten einen M.h.n. mit Thromben- oder Konkrementbildung durch eingedickte Galle. Ein Teil der Kinder waren Frühgeborene, bei denen eine Galleindickung, wahrscheinlich infolge Funktionsschwäche der Leber und Dehydrierung vorlag.

Über eine eigene Beobachtung mag an dieser Stelle kurz berichtet werden:

A. Sch., geb. 17.3.1955, Geb.-Gew. 3400 g. Klinikaufnahme: 19.3.1955.

Vorgeschichte: Es handelt sich um das erste Kind gesunder Eltern im Alter von 25 bzw. 23 Jahren. Es geht keine Fehlgeburt voraus. Die Mutter hat keine Transfusionen erhalten. Die Schwangerschaft verlief ohne Zwischenfall; die Geburt wurde durch vorzeitigen Blasensprung und lange Dauer kompliziert. Das Kind war nach der Geburt asphyktisch. Am 2. Lebenstag wurde es ikterisch, verweigerte jede Nahrung und hatte kurzdauernde Zuckungskrämpfe aller Extremitäten.

Aufnahmebefund (im Alter von 2 Tagen): Gewicht 3280 g, Temperatur 38°C, starker Ikterus und Cyanose, welker Turgor, keine Ödeme, keine Haut- und Schleimhautblutungen, leichte Conjunctivitis, Atmung unregelmäßig, Herz o.B., Milzpol als derber glatter, den Rippenbogen um einen Querfinger überragender Tumor tastbar, Leber o.B., Fontanelle $1\frac{1}{2}$ mal 2 Querfinger, nicht vorgewölbt, Krampfbereitschaft, kurzdauernde klonisch tonische Krämpfe der Extremitäten. Blut: Hb 101 % nach Sahli, Erythrocyten 5,6 Mill., am 4. Lebenstage Hb 140 % nach Sahli, Erythrocyten 6,8 Mill., im Ausstrich 20 % Erythroblasten. WaR und Nebenreaktionen negativ. Urin o.B.

Diagnose: Verdacht auf perinatale Hirnblutung, Erythroblastose?

Therapie: ACC 76 i.v. (Acceleratorfaktoren VI u. VII), Vit. K₁, Sauerstoff, Analeptica.

Blutformeln (22.3.1955):

Vater	A ₂ ccDE	Genformel cDE/cde
Mutter	O CeDee	Genformel CDe/cde
Kind	A ₂ ccDE	Genformel cDE/cde

Serum der Mutter zeigt im Konglutinationstest schwache Reaktion mit O cDE/cde Blutkörperchen. Direkter Coombstest beim Kind negativ.

Verlauf: Ikterus vom Verdintyp weiter zunehmend, Temperaturen normal, Hb-Wert am Ende der 3. Lebenswoche noch 126 % nach Sahli, Erythrocyten 6 Mill., zu Beginn der 9. Lebenswoche 85 % nach Sahli bzw. 4 Mill. Erythrocyten. Nahrungsaufnahme anfangs nur mittels Sonde möglich, später wechselnd, meist schlecht. Stühle ab 3. Lebenswoche von heller bis zitronengelber Farbe, aber nicht völlig acholisch, Urin d'gelb, aber nicht braun. Bei gleichzeitigem Verschwinden des Milztumors zunehmende Leberschwellung, die schließlich den Rippenbogen um 3 Querfinger überragt. Fortschreitende Dystrophisierung. Im Verlauf des 2. Lebensmonats erreicht der Ikterus seinen Höhepunkt. Neurologisch ist das Kind jetzt unauffällig. Krämpfe werden nicht mehr beobachtet. Im Urin werden ab 5. Woche die bisher normalen Urobilinogen-Proben auch bei wiederholter Untersuchung negativ. Bilirubin im Urin positiv. Eiweißreaktionen opal. Die Leberfunktionsprüfungen fallen sämtlich negativ

aus. Gesamteiweiß im Serum 6,54 g %, Gesamtbilirubin im Serum 13,64 mg % (direkt 2,74 mg %). Der Duodenalsaft ist farblos und trüb; Bilirubin und Gesamtcholesterin sind stark vermindert, Gallensäuren nicht nachweisbar.

Auf Grund des bisherigen Verlaufes und der erhobenen Befunde wird wegen Verdachts auf einen Gallengangverschluss am 26.5.1955 nach Vorbereitung eine Probelaparotomie durchgeführt. Dabei zeigt sich, daß die anatomischen Verhältnisse ausserhalb der Leber normal sind. Der Choledochus ist durchgängig. Die Leber selbst ist groß, derb und ikterisch. Die histologische Untersuchung des exzidierten Lebergewebes ergibt, daß die Gallenkapillaren vielfach mit Gallenthromben verstopft sind. Hochgradige Ablagerung von Gallenpigment in den Leberzellen. Erheblicher Parenchymschaden und Zelluntergang. Als Ursache der Veränderungen wird ein Resorptions-ikterus im Gefolge eines Retentionsikterus angenommen.

Am 2. Tag nach der Operation kommt das Kind infolge Kreislaufschwäche ad exitum. Gewicht 3580 g. Die Sektion bestätigt den bereits bei der Probelaparotomie erhobenen Befund eines schweren Ikterus und Leberparenchymschadens bei durchgängigen großen Gallenwegen. Von einer Hirnsektion wurde auf Wunsch der Eltern Abstand genommen.

Epikritisch handelte es sich demnach um einen Fall von Rh-Inkompatibilität ohne hervortretende pathologische Hämolyse, aber mit einem intrahepatischen Verschlussikterus infolge Verstopfung der Gallenkapillaren mit Gallenthromben. Der klinische Verlauf und die Laboratoriumsbefunde ließen den Ausschluß eines extrahepatischen Okklusionsikterus nicht zu, sodaß in der 10. Lebenswoche eine Probelaparotomie durchgeführt werden mußte, nach der das Kind ad exitum kam. Die äußeren Gallenwege waren frei.

Trotz der begründeten Forderung nach einer operativen Klärung der lokalen anatomischen Verhältnisse von einem bestimmten Zeitpunkt der Erkrankung an mahnt das Risiko des für den jungen und durch den langdauernden Ikterus vorgeschädigten Säugling sicher nicht gleichgültigen Eingriffs doch zu einer überlegten und strengen Indikationsstellung. Natürlich ist die Situation dann besonders zugespitzt, wenn Blutgruppen-Inkompatibilität und echte Mißbildung, also eine Atesie oder Agenesie der großen Gallenwege zusammentreffen. Daß es diese Kombination gibt, haben wir selbst kürzlich in zwei Fällen gesehen. Auf Grund dieser Erfahrung neigen wir jetzt zu der Auffassung, im Zweifelsfalle die informierende chirurgische Inspektion eher einmal mehr zu wagen als die spontane Rückbildung der Gelbsucht über den 4. Lebensmonat hinaus abzuwarten.

Wir möchten nun eine knappe Schilderung des Krankheitsverlaufs bei den beiden Kindern folgen lassen, die nach dem oft zitierten „Gesetz von der Duplizität“ in kurzem Abstand in unserer Klinik zur Aufnahme kamen.

R. L., geb. 23.11.1954, Geb.-Gew. 4250 g, Klinikaufnahme: 10.3.1955.

Vorgeschichte: Der Patient ist das dritte Kind gesunder Eltern im Alter von 24 Jahren. Das erste Kind ist gesund, das zweite war eine Fehlgeburt m. III. Die Schwangerschaft verlief normal und dauerte zwei Wochen über den errechneten Termin. Die Geburt war komplikationslos. Das Kind war bereits bei der Geburt ikterisch und hatte Ödeme. Nach zwei Wochen klang die Gelbsucht ab, die Ödeme wurden aus-

geschwemmt und das Kind blieb in der Folgezeit bei gutem Gedeihen unauffällig. Im Alter von zwei Monaten trat erneut eine Gelbsucht auf. Gleichzeitig wurden die Stühle weiß und der Urin dunkel. Dieser Zustand änderte sich nicht mehr bis zur Einweisung in die Klinik.

Aufnahmebefund (im Alter von 3½ Monaten): Gewicht 5470 g, Temperatur normal, guter Allgemeinzustand. *Intensiv ikterisches Kolorit* der Haut, Schleimhäute und Skleren. Keine Haut- und Schleimhautblutungen, keine Ödeme. Fontanelle 1 mal 1 Querfinger, nicht gespannt. ZNS unauffällig. Herz o.B. *Schwellung der Leber und Milz*, die beide den Rippenbogen um 2 Querfinger überragen. *Stühle acholisch* („wie Griesbrei“). *Urin dunkel*, Eiweiß 0, Zucker 0, *Urobilinogen 0/0*, Bilirubin +, Sediment o.B., Blut: *Hämoglobin 66 % n. Sahli*, *Erythrocyten 3,2 Mill.*, Leukocyten 9200, Differentialblutbild normal, *Gesamtbilirubin im Serum 9,7 mg % (direkt 8,2 mg %)*, Gesamteiweiß 6,12 g %. WaR und Nebenreaktionen negativ. Die Leberfunktionsprüfungen fallen sämtlich negativ aus. Blutungs- und Gerinnungszeit sind normal, die Erythrocytenresistenz ist erhöht.

Blutformeln (14.3.1955):

Vater	A ₁ ccDEe	Genformel cDE/cde
Mutter	A ₁ ccee	Genformel cde/cde
Kind	A ₁ CcDEe	Genformel cDE/CDe

Serum der Mutter enthält inkomplette *Antikörper vom Typ Anti-D* mit einem Titer von 1:4.

Diagnose: Rh-Inkompatibilität, Verschlußikterus.

Da die Entscheidung, ob es sich im vorliegenden Falle um einen intrahepatischen Verschluß durch Gallenthromben bei M.h.n. oder um eine Mißbildung der großen Gallengänge handelt, ohne chirurgischen Eingriff nicht gefällt werden kann, entschließt man sich zur Probelaparotomie, die am 21.3. durchgeführt wird.

Operationsbericht (Dr. Wollmann): In Äthernarkose Eröffnung der Bauchhöhle durch Transrektalschnitt rechts oben. Die Leber ist stark vergrößert und reicht fast 3 Querfinger über den Rippenbogen. Die Gallenblase ist ebenfalls stark vergrößert, prall gespannt und überragt den vorderen Leberrand um Daumenbreite. Der Choledochus ist auf Fingerdicke erweitert, prall gefüllt und infolge bindegewebiger Einziehungen mehrfach ausgebuchtet. Er wird nach vorhergehender Punktion, die etwa 5 cm klarer Galle ergibt, bis an das Duodenum längs inzidiert. Versuche, den Choledochus in das Duodenum zu sondieren, mißlingen. Der atretische Stumpf wird ausgetupft und enthält grünliche Galle mit einigen dunklen Niederschlägen, aber kein Konkrement. Sodann wird die Vorderwand des Duodenum unterhalb des Pylorus inzidiert und eine Anastomose zwischen Choledochus und Duodenum in typischer Weise hergestellt. Ein Drain wird in das Foramen epiploicum gelegt und die Bauchhöhle verschlossen. Das Drain wird rechts seitlich durch die Bauchwand herausgeleitet.

Verlauf: Nach der Operation treten hohe Temperaturen auf, die innerhalb einer Woche lytisch zur Norm abfallen. Gewichtssturz bis 5100g. Behandlung mit Infusionen, Antibiotica, Vitamin A, D und K. Am 4. Tag post operationem wird spontan der erste gefärbte Stuhl entleert. Der weitere Verlauf ist komplikationslos. Am 23.4. kann das Kind mit einem Gewicht von 6040 g nach Hause entlassen werden.

Am 1.6.1955 kommt es nochmals zu einer klinischen Nachuntersuchung. Es hat sich in der Zwischenzeit sehr gut entwickelt und wiegt jetzt 6830 g. Organisch ist das Kind befundfrei und macht einen völlig gesunden Eindruck. Hb 96 % nach Sahli, Erythrocyten 4,6 Mill.

Epikrise: Bei dem vier Monate alten Kind bestand eine serologisch gesicherte Rh-Inkompatibilität mit ikterischem Verschußsyndrom. Da die differentialdiagnostische Entscheidung zwischen einem intra- oder extrahepatischen Verschuß ohne chirurgischen Eingriff nicht möglich war, wurde das Kind laparotomiert. Dabei konnte eine Gallengangsatresie nachgewiesen und die Heilung durch Anlegen einer Anastomose zwischen D. choledochus und Duodenum erzielt werden.

H. G. K., geb. 5.4.1955, Geb.-Gew. 3600 g., Klinikaufnahme: 9.5.1955.

Vorgeschichte: Es handelt sich um das zweite Kind gesunder Eltern im Alter von 24 bzw. 20 Jahren. Das erste Kind hat sich normal entwickelt. Die Schwangerschaft verlief ohne Besonderheiten, die Geburt war normal. Am 17. Lebenstag trat eine stärkere Nabelblutung auf, die die Einweisung in ein Krankenhaus erforderlich machte, wo der Nabel chirurgisch versorgt wurde und das Kind eine Transfusion erhielt. Kurz vor der Krankenhauseinweisung waren erstmalig *acholische Stühle* bemerkt worden, während eine *zunehmende ikterische Verfärbung* der Haut erst jetzt beobachtet wurde. Fieber bestand nicht. Da der nach der Transfusion vorübergehend auf 75 % angestiegene Hb-Wert erneut absank und das Kind schlecht gedieh, erfolgte nun die Verlegung in unsere Klinik.

Aufnahmebefund (im Alter von 5 Wochen): Gewicht 3700 g, Temperatur 39°C. Mäßiger Allgemeinzustand. Haut, Schleimhäute und Skleren zeigen ein deutlich *ikterisches Kolorit* bei ausreichendem Hautturgor. Keine Blutungen, keine Ödeme. Fontanelle 2mal 2 Querfinger, ZNS o. B. Herz o. B. Deutliche *Leber- und Milzschwellung*. Erstere reicht 2, letztere 1 Querfinger über den Rippenbogen. Die *Stühle* sind *acholisch*, der Urin ist hellbraun. Eiweißprobe opal, Zucker 0, *Urobilinogen* 0/0, Bilirubin +, Sediment o. B. Blut: Hb 59 % n. Sahli, *Erythrocyten* 3 Mill., Leukocyten 8600, Differentialblutbild ohne Besonderheiten, *Gesamtbilirubin im Serum* 6,35 mg % (*direkt* 4,12 mg %), Gesamteiweiß im Serum 7,2 g %, WaR und Nebenreaktionen negativ. Die Leberfunktionsprüfungen sind negativ; Blutungs- und Gerinnungszeit, sowie Erythrocytenresistenz sind normal.

Blutformeln (10.5.1955):

Vater	O ccee	Genformel cde/cde
Mutter	A ₁ CCDee	Genformel CDe/CDe
Kind	A ₁ CcDee	Genformel CDe/cde

Serum der Mutter zeigt im Konglutinationstest eine schwache Reaktion mit den Blutkörperchen des Kindes und des Vaters. Es liegt möglicherweise ein schwaches, inkomplettes *Anti-c* vor.¹

Diagnose: Verdacht auf Morbus haemolyticus neonatorum. Verschußikterus.

Nachdem die differentialdiagnostisch wichtige Frage nach dem Vorliegen eines Obstruktionsikterus infolge eines möglichen M.h.n. bzw. einer Mißbildung der extrahepatischen Gallenwege ohne Inspektion der lokalen Verhältnisse nicht beantwortet werden kann, wird am 23.5. eine Probepaparatomie ausgeführt.

Operationsbericht (Dr. Wollmann): In Äthernarkose Eröffnung der Bauchhöhle durch Transrektalschnitt rechts oben. Es besteht eine starke biliäre Schwellung der Leber. Freilegung der viszerale Leberfläche, des Duodenum und des Ligamentum

¹ Die Untersuchungen wurden vom Direktor des Staatl. Mediz. Untersuchungsamtes in Braunschweig, Herrn Medizinalrat Dr. L. Popp durchgeführt, dem wir an dieser Stelle für seine Mitarbeit danken möchten.

hepatoduodenale. Es zeigt sich, daß eine völlige Aplasie der äußeren Gallenwege besteht. Man findet weder eine Gallenblase, noch einen D. choledochus, noch einen D. hepaticus. Der Eingriff muß daher ergebnislos abgebrochen werden. Die Bauchhöhle wird primär verschlossen.

Verlauf: Vorübergehende Temperaturerhöhung nach der Operation. Behandlung mit Infusionen, Antibiotica, Vitamin A, D und K. Primäre Heilung der Operationswunde und Entlassung des Kindes in weitere häusliche Pflege am 21.6.1955 bei einem Gewicht von 3520 g.

Erneute Aufnahme des Patienten in stationäre Behandlung am 19.1.1956. Das Kind macht jetzt einen stark dystrophisierten Eindruck. Es wiegt 5950 g (!). In seiner statischen und *geistigen Entwicklung* ist es weit zurückgeblieben. *Kopfumfang* 42 cm. Fontanelle 3mal 3 Querfinger. *Hydrocephalus?* Intensiver Verdikterus der Haut, Schleimhäute und Skleren. Starke Ödeme, besonders der unteren Körperpartien. Herz u. Lunge o.B. Der Bauch ist bei vermehrter Venenzeichnung mächtig vergrößert und sehr gespannt, der Nabel verstrichen. Reizlose Narbe nach Laparotomie. Aszites. Die Leber reicht 3 Querfinger über den Rippenbogen, ist höckerig und hart. Die Milz ist nicht tastbar. Stühle acholisch, Urin d' gelb, Eiweißprobe opal, Urobilinogen 0/(+), Sediment o.B., Bilirubin +. Blut: Hb 42 % nach Sahli, Erythrocyten 2,5 Mill., Leukocyten 8200.

Trotz allen Bemühungen, durch Stützung des Herzens und Anregung der Diurese den Zustand zu verbessern, kommt das Kind am 5.2.1956 ad exitum. Eine Sektion wird verweigert.

Epikrise: Beim zweiten Kind einer Rh-konstellierten Familie bestand der klinische Verdacht einer Inkompatibilität mit gleichzeitigem Verschlußikterus. Zur Klärung der laboratoriumstechnisch nicht sicher zu beantwortenden Frage, ob eine Mißbildung oder ein Rh-bedingter Verschluß bestand, wurde eine Probelaparotomie durchgeführt. Diese deckte eine völlige Aplasie der äußeren Gallenwege auf. Das Kind verstarb später infolge einer biliären Cirrhose. Der Nachweis eines Kernikterus war nach Ablehnung der Sektion nicht möglich.

Besprechung

Lightwood und Bodian haben sich vor zehn Jahren mit der bis dahin bekannt gewordenen Kasuistik eines gemeinsamen Auftretens von M.h.n. und Gallengangsatriesie kritisch auseinander gesetzt. Es waren insgesamt vier von Pasachoff (1935), Sanford (1940) sowie Skelton u. M. (1945) veröffentlichte Fälle.

Bei dem ersten (Pasachoff) handelte es sich um einen am 5. Lebenstag verstorbenen Säugling, der bereits 12 Stunden nach der Geburt einen intensiven Ikterus, eine Hepatosplenomegalie und eine Erythroblastose ohne Anämie zeigte. Letztere entwickelte sich in mäßigem Grade erst nach Auftreten von Hämorrhagien am 4. Lebenstag, an dem auch acholisches Stühle entleert wurden. Die Sektion ergab den Befund einer ausgedehnten extramedullären Hämatopoese, eines Kernikterus und einer kompletten Atriesie der Gallengänge. Die Diagnose „Ikterus gravis“ konnte serologisch nicht untermauert werden, da sich das Geschehen in der Vor-Rhesus-Zeit abspielte.

Der zweite von Sanford berichtete Fall betraf ein Kind, das bereits 2 Stunden post partum eine schwere Anämie mit Erythroblastose und einen Ikterus gravis hatte. Bei der Sektion wurde eine Atriesie bzw. weitgehende Stenose der großen Gallengänge nachge-

wiesen. Der Vater des Kindes war Rhesus-positiv, die Mutter rhesus-negativ. Ein zwei Jahre später geborenes Rhesus-positives Kind hatte einen typischen M.h.n. Die Blutformel des Patienten selbst war nicht bestimmt und ebensowenig der Nachweis von Antikörpern im mütterlichen Blut erbracht worden.

Skelton u. M. berichten über die restlichen beiden Fälle. Der eine betraf ein Zweitgeborenes mit Gelbsucht am ersten Lebenstag. Nach dem zwei Tage später erfolgten Exitus deckte die Sektion eine Erythroblastose mit extramedullärer Hämatopoese, einen Kernikterus und eine Choledochusatresie auf. Der Vater und das erstgeborene Kind waren Rhesus-positiv, die Mutter rhesus-negativ. Das verstorbene Kind war nicht getestet worden. Mütterliche Antikörper waren 3 Jahre nach dem Vorkommnis nicht mehr nachweisbar.

Bei dem letzten handelte es sich wieder um ein zweitgeborenes Kind. Ein Ikterus am ersten Lebenstag, Bilirubinurie und acholische Stühle charakterisierten das klinische Bild. Bei einem späteren Eingriff konnte eine Choledochusatresie operativ behoben werden. Kind und Vater waren Rhesus-positiv, die Mutter rhesus-negativ. Zwei später geborene Kinder verstarben infolge eines M.h.n. Bei diesen Geburten gelang der Nachweis mütterlicher Antikörper, der zur Zeit der Geburt des zweiten Kindes nicht geführt worden war. Verff. erwähnen noch ein ähnliches Vorkommnis, wobei in einer Rh-konstellierten Familie das dritte Kind infolge Gallengangsatresie und das sechste Kind im Verlauf eines M.h.n. verstorben waren.

Lightwood schildert in diesem Zusammenhang noch einen von ihm selbst gesehenen Fall.

Dieser Patient war als drittes Kind nach zwei gesunden Geschwistern geboren worden. Am dritten Lebenstag war eine Gelbsucht aufgetreten, die nach 8 Tagen wieder abklang. Im Alter von 6 Wochen wurde das Kind anämisch (1,5 Mill. Erythrocyten, 4,8 g % Hb). Zugleich wurde es wieder ikterisch (Van den Bergh 6,7 mg %). Die Stühle entfärbten sich und im Urin war Gallenfarbstoff nachweisbar. Zu Beginn des 3. Lebensmonats wurde serologisch eine Rh-Konstellation festgestellt und dem Kind rhesus-negatives Blut transfundiert. Antikörper waren bei der Mutter nicht mehr nachweisbar. Nach der Transfusion besserte sich die Anämie, doch blieb die Gelbsucht unverändert bestehen. Es wurde eine Laparotomie ausgeführt, bei der sich eine inoperable Atresie der großen Gallenwege fand. Das Kind verstarb 7 Tage nach dem Eingriff. Es war 4½ Monate alt geworden. Die Sektion ergab außer der beschriebenen Mißbildung eine biliäre Cirrhose der Leber mit Verschluß der interzellulären Gallengänge durch Gallenthromben.

Diese Krankengeschichte zeigt Ähnlichkeiten mit unseren eigenen zuvor referierten Fällen, als Besonderheit aber das gleichzeitige Vorkommen eines intra- und extrahepatischen Verschlusses. Wegen des fehlenden Nachweises einer Immunisierung des mütterlichen Serums kommt Lightwood zu dem sehr zurückhaltenden Schluß, daß auch dieser Fall ebenso wie die aus der Literatur zitierten keinen Beweis für das gleichzeitige Auftreten von M.h.n. und Gallengangsatresie liefere, sondern nur gewisse Verdachtsmomente für eine solche Möglichkeit biete. Seine Zweifel zielen allerdings immer in Richtung einer *ätiologischen Verbindung* der beiden Krankheitsbilder, die er ablehnen zu müssen glaubt. Darin möchten wir ihm durchaus beipflichten.

Wir haben bei der Beurteilung unserer beiden Fälle, denen im Vergleich zu der Gesamtzahl der Inkompatibilitäten des Rh-Systems lediglich ein Seltenheitswert zukommt, keinen Augenblick an die Möglichkeit eines kausalen Zusammenhanges gedacht etwa in dem Sinne, daß eine Rh-Inkompatibilität als ätiologischer Faktor für das Zustandekommen einer kongenitalen Gallengangsatresie oder -agenesie in Frage käme. Das schließt aber ein *zufälliges Zusammentreffen* der beiden Erkrankungen nicht aus.

Man wird in diesem Zusammenhang an die ebenso zufällige Kombination von Rh-Konstellation und cystischer Pankreasfibrose erinnert, die Glanzmann eine ätiologische Beziehung zwischen beiden annehmen ließ. Wir wissen heute, daß eine solche nicht besteht.

Nachdem anscheinend auch diskrete Verlaufsformen eines M.h.n. zur Obstruktion der interzellulären Gallengänge führen können, werden unter Umständen schon der Nachweis einer vorliegenden Rh-Konstellation und gewisse klinische Verdachtszeichen wie in unserem zweiten Fall genügen, um die differentialdiagnostische Situation zu komplizieren. Auf die Schwierigkeiten in der Diagnostik solcher Fälle hinzuweisen, war unser Anliegen, als wir uns zur Veröffentlichung obiger Krankengeschichten entschlossen.

Tatsächlich ist eine Trennung der beiden Verschlußsyndrome mittels klinischer und Laboratoriumsuntersuchungen allein kaum möglich. Beginn und Farbtyp des Ikterus geben ebensowenig einen sicheren Anhalt wie das Verhalten von Bilirubin und Urobilinogen im Harn. Die Stühle sind immer mehr oder weniger entfärbt; Zumindest spricht eine unvollständige Entfärbung nicht gegen eine Mißbildung (van Creveld, Žucha, Catel). Leber- und Milzschwellung sind sowohl beim M.h.n. als auch beim Gallengangsverschluß möglich. Auch das Blutbild gibt keinen verlässlichen Hinweis, da einerseits eine Rh-Inkompatibilität mit normalen Blutwerten, andererseits eine reine Gallengangsmißbildung mit erheblicher Anämie einhergehen kann (Lightwood). Die üblichen laboratoriumstechnischen Prüfmethode (Eiweißfraktionen, Cholesterinspiegel, Flockungsteste, Gallensäuren u. a.) ergeben keine differentialdiagnostisch zuverlässigen Befunde. Daß auch die Bestimmung der alkalischen Serumphosphatase nicht immer weiterhilft, wurde von verschiedenen Seiten betont (Kiesewetter, Lightwood). Einen brauchbaren Hinweis kann das Verhalten des Serumbilirubins geben, dessen direkter Anteil beim extrahepatischen Okklusionsikterus immer stark vermehrt ist. Die von uns referierten Fälle bestätigen diese Auffassung ebenfalls. Zu der Frage, ob ein langsamer bzw. rascher Anstieg der Bilirubinämie differentialdiagnostisch verwertbar ist (Hsia, Kiesewetter), können wir uns aus eigener Erfahrung nicht äußern. Harris u. M. sprechen der Biopsie und Cholangiographie einen Wert als diagnostisches Hilfsmittel zu.

Am überzeugendsten kann natürlich das Verschwinden des Verschlußsyndroms die Situation klären. Im allgemeinen bildet sich der Obstruktionsikterus beim M.h.n. spätestens nach wenigen Monaten restlos zurück (Salomonsen, Hsia u. M.). Da dies aber nicht zwangsläufig bis zum Beginn des zweiten Trimenon erfolgen muß, bei einem Teil der Betroffenen die Verstopfung der Gallenkapillaren zudem bestehen bleibt, um schließlich zum Leberparenchymschaden und zur cirrhotischen Umwandlung des Organs zu führen, wird auch ein vorläufiges Abwarten und Zurückstellen aller chirurgischen Maßnahmen nicht immer zum Ziele führen. Vereinzelt konnte auch die Bildung größerer Konkreme (Pigmentsteine) im Anschluß an die obstruktive Phase des M.h.n. beobachtet werden, sodaß es nach deren Abklingen sekundär zum Verschluß der großen Gallengänge kommen kann (Lightwood, Hsia u. M.).

Über den äußersten Zeitpunkt einer operativen Klärung des lokalen Befundes gehen die Meinungen etwas auseinander. Während Žucha den Eingriff bereits am Ende des ersten Lebensmonats befürwortet, empfehlen Harris u. M. seine Durchführung „bis zum vierten Monat spätestens“. Moore wünscht die Operation „nicht erst im Alter von 4½ Monaten“ und Hsia rät ganz allgemein, sie „nicht zu spät“ vorzunehmen. Jedenfalls scheint ein über den vierten Lebensmonat hinausgehendes Zögern wegen der damit verbundenen Gefahr der Entwicklung irreparabler Schäden nicht angezeigt.

Leider gestatten die anatomischen Verhältnisse nur bei einem Bruchteil aller Mißbildungen der äußeren Gallenwege die Anlegung einer Anastomose. Im günstigsten Falle kann ein Viertel der betroffenen Kinder durch die Operation gerettet werden (Žucha, Dahl u. M., Ladd, Kiesewetter u. M., Hsia u. M.).

Zusammenfassung

Die Abgrenzung des intrahepatischen Obstruktionsikterus beim Morbus haemolyticus neonatorum von dem Verschlußsyndrom bei Atresie der großen Gallengänge ist äußerst schwierig. Sie wird häufig erst durch eine Laparotomie möglich sein. Zu deren rechtzeitiger Durchführung muß um so mehr geraten werden, als eine Gallengangsmissbildung mit einer Rh-Inkompatibilität vergesellschaftet sein kann.

Über zwei derartige Fälle wird berichtet. Bei dem einen handelte es sich um eine Atresie des D. choledochus bei M.h.n. Das Kind konnte operativ durch Herstellung einer Anastomose zwischen Gallengang und Duodenum geheilt werden. Im anderen Falle lag eine Agenesie der äußeren Gallenwege bei gleichzeitiger Rh-Konstellation mit Verdacht auf einen M.h.n. vor. Dieses Kind verstarb nach 10 Monaten infolge einer biliären Cirrhose.

Nach einem Rückblick auf ähnliche aus der Literatur bereits bekannte Zufälle wird die differentialdiagnostische Problematik kurz besprochen.

Malformation of the bile ducts and Rhesus incompatibility.

Differentiation between intrahepatic obstructive jaundice as seen in haemolytic disease of newborn and the obstructive syndrome seen in the case of atresia of the large bile ducts is extremely difficult. It is often not possible until an exploratory laparotomy is resorted to. Early laparotomy is especially advisable because a malformation of the bile ducts can be associated with Rhesus incompatibility. Two cases showing this association are described. One case involved atresia of the common bile duct associated with haemolytic disease of newborn. The child was surgically cured by an anastomosis between the bile duct and the duodenum. In the other case there was agenesis of the external bile ducts associated with a Rhesus constellation suggestive of haemolytic disease of newborn. The child died 10 months later as a result of biliary cirrhosis. The problems of differential diagnosis are briefly discussed after a review of similar incidental findings reported in the literature.

Malformation des voies biliaires et Rhesus-incompatibilité.

La délimitation entre l'ictère intrahépatique par rétention en cas de maladie hémolytique des nouveaux-nés et le syndrome d'obstruction dans l'atrésie des grandes voies biliaires est extrêmement difficile. Il est fréquent que, seule, une laparotomie d'essai la rende possible. Il faut d'autant plus conseiller de pratiquer cette intervention à temps parce qu'une malformation des voies biliaires peut être accompagnée d'une Rh. incompatibilité. L'auteur communique deux cas : L'un d'eux concerne une atrésie du canal cholédoque lors de maladie hémolytique du nouveau-né. L'enfant fut sauvé par une opération qui consiste à établir une anastomose entre le canal cholédoque et le duodénum. Il y avait dans l'autre cas une agénésie des voies biliaires extérieures en même temps qu'une Rh. constellation et suspicion d'une M.h.n. L'enfant succomba 10 mois plus tard par suite d'une cirrhose biliaire. Après avoir passé en revue des cas de ce genre déjà connus dans la bibliographie, l'auteur discute brièvement des difficultés du diagnostic différentiel.

Deformidad del conducto biliar y Rheso-incompatibilidad.

La delimitación de la ictericia obstructiva intrahepática en la enfermedad hemolítica del recién nacido del síndrome de oclusión en la artresia de los grandes conductos biliares, es extremadamente difícil. Con frecuencia, solamente es posible por medio de una laparatomía de exploración. Por lo tanto deberá aconsejarse su ejecución a tiempo, ya que una malformación del conducto biliar puede ir acompañada con una incompatibilidad Rh. El autor presenta dos casos: en uno de ellos se trataba de una atresia del colédoco con enfermedad hemolítica neonatal. El niño se curó por medio de una operación en la que se estableció una anastomosis entre el conducto biliar y el duodeno. En el otro caso el niño presentaba una agenesia de los conductos biliares exteriores con simultánea constelación Rh y sospechas de enfermedad hemolítica del recién nacido. Este niño murió después de 10 meses a consecuencia de una cirrosis biliar. Después de considerar retrospectivamente casos análogos ya conocidos en la literatura se discute brevemente el problema del diagnóstico diferencial.

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On the Occurrence of Adenoviruses in Sweden

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In the course of a study of some 800 stool specimens obtained in Stockholm during the epidemic of poliomyelitis in 1953 (21) five strains of adenoviruses were encountered. Similar agents were recovered from the stools of three patients with the diagnosis of mesenteric lymphadenitis. In one of these cases the virus was also isolated from a mesenteric lymph node. The results of a detailed study of these first Swedish strains of adenoviruses have been reported previously (13). It was thus found that all strains shared complement fixing antigens with each other as well as with the agent RI-67 isolated by Hilleman & Werner (10) and with the Sutherland strain isolated by Neva & Enders (17). By neutralization tests on the other hand, the strains were separated into three groups. Other studies in the laboratory of Huebner (11) have established that these types of viruses can be classified together with agents isolated by them from various sources. The first report on such viruses thus seems to be that of Rowe and co-workers (19) on agents recovered from human adenoids. Various names for this virus group have been used by different authors, including APC (adenoidal-pharyngeal-conjunctival, (11)), RI (respiratory illness, (10)), and ARD (acute respiratory disease, (7)) viruses. Recently the term Adenoviruses was agreed upon (5). Seventeen serologically distinct types of adenoviruses have so far been reported (18). By epidemiological, clinical and laboratory studies some types have, more or less definitely, been etiologically correlated to syndromes of human disease, such as various types of respiratory illnesses (10, 2, 7, 3, 4) and kerato-conjunctivitis (12).

The present paper is a report on the various strains of adenoviruses isolated in Sweden since 1953. Extensive data will be given only in those cases where type 7 virus was isolated. The outbreaks of type 3 adenovirus

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infections briefly referred to in this communication will be described in detail in other reports (15, 1) were clinical, epidemiological and laboratory observations will be presented.

Materials and methods

Several approaches have been tried in our search for members of the adenovirus group. Since the first isolation in 1954 of an adenovirus strain from a mesenteric lymph node, 113 cases of mesenteric lymphadenitis have been similarly examined. Mesenteric lymph nodes were tested from 96 of them, stool specimens from 82. Details of the various virus findings will be given in another connection (16).

During the fall of 1954 and early 1955 specimens from about 50 children suffering from pneumonia were examined. The etiology in most of these cases was unknown. Later in 1955 when it was evident that very few adenoviruses were recovered from this material we undertook a study of a group of children hospitalized for undifferentiated upper respiratory infections.

Most type 3 infections mentioned in this paper occurred in the summer and fall of 1955. Thus an epidemic of "pharyngoconjunctival fever" (2) in the small town of Kumla in the middle of Sweden was studied (15). In connection with this outbreak the spread of nosocomial infections with the same type of virus was followed among children at the Hospital for Infectious Diseases in the town of Örebro not far from Kumla (1).

Some of our adenovirus strains were recovered from stool specimens tested in tissue culture for various other reasons, such as a suspected poliomyelitis infection. Most of them were isolated during a study of an outbreak of poliovirus type 3 infections which occurred at a combined orphanage and nursery school in Stockholm in the fall of 1955 (9).

Collection of specimens.—The intention has been to get an early sample of materials suitable for virus isolation from each patient (i.e. stool, occasionally nasopharyngeal swab, conjunctival swab or mesenteric lymph nodes). However, the specimens were actually taken within a rather wide range of time after onset of disease. Stool specimens were obtained from almost all patients. The mesenteric lymph nodes were removed in connection with appendectomies at Kronprinsessan Lovisas Barnsjukhus, Stockholm. We are much indebted to Docent Gunnar Ekström and his staff for their cooperation.

Acute phase serum as well as a convalescent sample about 2 weeks later were regularly asked for but not always possible to obtain.

The specimens were stored at a temperature of -20° to -25°C until used.

Tissue cultures.—Roller tube cultures of human embryonic lung and of HeLa cancer cells were employed. All passages and typings were performed in the latter type of cultures. Cultures were set up and maintained according to techniques described previously (21, 13). Bovine amniotic fluid (BAF) with the addition of 50–100 IU penicillin and 50–100 μg streptomycin per ml was used as a maintenance medium after virus inoculation. Since 1955 0.5 per cent Bacto tryptose has been incorporated (8).

Virus isolations.—*Stools:* A 10 per cent suspension in BAF containing 500 IU penicillin and 500 μg streptomycin per ml was prepared. After centrifugation at 3500 r.p.m. for 30–60 minutes 0.1–0.2 ml of the supernatant was inoculated into each of

3 roller tubes of either HeLa cells or human embryonic lung or, in most cases, into three tubes of each type.

Swabs: the nasopharyngeal and conjunctival swabs were usually sent to the laboratory immersed in 1-2 ml nutrient broth or aqua dest. After addition of antibiotics the fluids were examined in the same way as the stool extracts.

Lymph nodes: each lymph node specimen was ground with a small amount of alundum together with 1-2 ml BAF containing 100 IU penicillin and 100 μ g streptomycin per ml. After clarification by centrifugation at 3500 r.p.m. for 30 minutes the extract was examined in the same way as the stool suspensions.

The microscopic appearance of the cultures was recorded twice a week for 2-3 weeks. When cytopathic changes were observed or suspected the fluid harvest was passed to new HeLa cell cultures. Where this secondary passage also showed cytopathic changes the fluid was harvested and tested for the presence of adenovirus by a complement fixation test against a known positive human serum. The strains were separated into types by neutralization tests with type-specific rabbit hyperimmune sera. As a routine a 1/10 dilution of the tissue culture harvest was mixed with equal amounts of suitable dilutions (usually 1/2) of hyperimmune sera against the seven first types of adenovirus. After incubation for 1 hour at room temperature 0.2 ml of each mixture was inoculated into two HeLa cultures. The single strain which was not neutralized by immune sera against any of the seven first types was also tested against types 9 and 10. The tissue culture harvests diluted 1/10 showed, fairly regularly, a cytopathic effect on the HeLa cells on the second to third day after inoculation. Heterologous immune sera had no obvious inhibiting effect whereas homologous sera, in the concentrations used, usually delayed the cytopathic changes for about 14 days. A control titration of the virus material was always performed in the same experiment.

Hyperimmune sera.—Rabbit sera were prepared against the 10 first types, type 8 excepted, in the scheme of Huebner and co-workers (11, 18). The following immunizing schedule was usually employed: 5 ml of a tissue culture harvest centrifuged at 3500 r.p.m. for 30 minutes was inoculated into the hind leg of a rabbit once a week three times. Three weeks after the third injection another 5 ml was given into the leg or, sometimes, intravenously. Ten days later the rabbits were bled by heart puncture. Some of the rabbits have subsequently been boosted one or several times before new bleedings. Adequate sera were easily and regularly obtained.

Neutralization tests.—The neutralization tests reported on in this paper were performed with sera collected from those patients who excreted adenovirus type 7. The following technic was used. Serum diluted 1/2 was mixed with an equal amount of a 1/10 dilution of a passage of strain no. 9415/55 (type 7). Undiluted this batch of virus titrated 10^{-7} , the end point being taken from the 14 day reading. After incubation at room temperature for 1 hour 0.2 ml of the mixture was inoculated into two HeLa cell cultures. The microscopic appearance was recorded each or each other day for 14 days. The relative inactivation capacity of a serum could be estimated by determination of the prolongation of the incubation period in the tubes containing immune sera. This technic was based upon the observation, described elsewhere (14), that there exists a linear relationship between the logarithm of the virus dose and the incubation time before the appearance of cytopathic changes. In the control titration of the type 7 strain the dilution 10^{-1} showed cytopathic changes on the second day after inoculation whereas the dilution 10^{-6} needed 13.5 days to cause the same extent of degeneration. If the serum-virus mixture caused cytopathic changes concomitantly with the virus control or one day later the serum was considered negative. A "break-through"

4-7 days after inoculation indicated the presence of definite amounts of neutralizing antibody in the serum and is recorded as +. If cytopathic changes did not occur until the second week (7-14 days) the serum is marked ++. +++ means that the final reading after 14 days was still negative.

Complement fixation tests.—The technic developed by Fulton & Dumbell (6) and modified by Svedmyr *et al.* (20) was used. As antigen we employed fluids from Roux flask cultures of HeLa cells infected with a type 5 strain (4574/54), inactivated at 56°C for 1 hour and clarified by low-speed centrifugation.

Results

Table 1 shows the type distribution of the adenovirus strains recovered in our laboratory. Only one strain (obtained from a child suffering from pharyngitis, conjunctivitis and adenitis cervicalis) was not neutralized by any of the immune sera available, i.e. types 1-7, 9 and 10.

Isolations of adenoviruses types 1, 2 and 5.—Table 2 summarizes the data of the patients from whom adenoviruses types 1, 2 or 5 were recovered. Various diagnoses were represented among those cases. The results of the CF test, when carried out, indicate that at least some of the patients, i.e. those with a rising titer, experienced an acute infection with the recovered virus simultaneously with the recorded symptoms. On account of the few and scattered cases and the absence of a suitable control material it is, however, so far not possible to draw any definite etiological conclusions in these cases. It should be recalled that these types of adenoviruses were frequently recovered by Huebner and co-workers (11) from tonsils and adenoid tissues of apparently normal children.

TABLE 1

Type distribution of 148 adenovirus strains isolated in Sweden 1953-56 from 112 patients and 2 samples of sewage water.

Virus type	Number of virus excretors	Number of pos. specimens	Type of specimens
1	5	6	Stools
2	12	15	Stools, nasopharyngeal swabs, mesenteric lymph nodes
3	63	82	Stools, nasopharyngeal swabs, conjunctival swabs
	—	2	Sewage water
5	15	20	Stools, mesenteric lymph node
7	17	22	Stools, nasopharyngeal swabs
4, 6, 9, 10	0	0	
Other types	1	1	Stool
Total	112	148	

TABLE 2

Data on patients from whom adenoviruses types 1, 2 or 5 were isolated.

Strains No. 10296 (type 5) and 11867 (type 1) were recovered from two different stool specimens obtained from the same patient.

Strain No.	Age of patient (years)	Clinical diagnosis	Isolation of adenoviruses					CF-antibodies against adenovirus	
			Virus type	Stool	Naso-pharynx	Conjunctival swab	Mesenteric lymph node	Serum 1	Serum 2
11865*	1.5	Rhinopharyngitis acuta	1	+	ND ¹	ND	ND	ND	ND
11810*	2	Healthy (excretor of poliovirus type 3)	1	+	ND	ND	ND	16	16
11867*	1.5	Rhinopharyngitis acuta	1	+	ND	ND	ND	ND	ND
11952	2	Rhinopharyngitis acuta	1	+	ND	ND	ND	ND	ND
12234	7/13	Conjunctivitis acuta + bronchitis asthmatica	1	+	ND	ND	ND	8	8
5895	5	Primary atypical pneumonia	2	+	ND	ND	ND	16	8
5935	9	Primary atypical pneumonia	2	-	+	ND	ND	4	8
6097	11/12	Encephalitis acuta + otitis simplex dxt.	2	+	ND	ND	ND	ND	ND
8097	3	Lymphadenitis mesenterii	2	+	-	ND	+	< 2	16
9036	5	Lymphadenitis mesenterii	2	+	-	ND	+	4	2
9070	1.5	Lymphadenitis mesenterii	2	+	-	ND	-	ND	8
10086	1	Status post poliomyelit. + impetigo contagiosa	2	+	ND	ND	ND	ND	ND
11896*	2.5	Pharyngitis acuta	2	+	ND	ND	ND	ND	ND
12097*	2	Rhinopharyngitis acuta	2	+	ND	ND	ND	ND	ND
12432	1	Nasopharyngitis acuta + pertussis	2	+	ND	ND	ND	< 2	< 2
12470	2	Nasopharyngitis acuta + pertussis	2	+	ND	ND	ND	< 2	32
XA 7	10	Pharyngitis acuta + otitis med. acuta	2	+	+	ND	ND	32	64
472	10	Pharyngitis acuta + sinusitis max. dxt.	5	+	ND	ND	ND	< 2	64
1836	19	Poliomyelitis acuta cum pares. spinal.	5	+	ND	ND	ND	4	2
2671	6	Pharyngitis acuta	5	+	ND	ND	ND	ND	64
4574	4	Lymphadenitis mesenterii	5	+	ND	ND	+	< 2	128
7551	22	Pharyngitis acuta + laryngitis acuta + conjunctivitis acuta	5	+	ND	ND	ND	< 2	2
10247	1.5	Pharyngitis acuta	5	+	ND	ND	ND	ND	ND

Table 2 (continued)

Strain No.	Age of patient (years)	Clinical diagnosis	Isolation of adenoviruses					CF-antibodies against adenovirus	
			Virus type	Stool	Naso-pharynx	Conjunctival swab	Mesenteric lymph node	Serum 1	Serum 2
10296*	1.5	Rhinopharyngitis acuta	5	+	ND	ND	ND	ND	ND
11662*	2	Pharyngitis acuta + conjunctivitis acuta (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11713*	1	Healthy (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11716*	1	Healthy (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11750*	2	Pharyngitis acuta (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11756*	1	Healthy (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11811*	1.5	Rhinopharyngitis acuta (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND
11790*	1	Healthy	5	+	ND	ND	ND	ND	ND
11795*	2	Healthy (excretor of poliovirus type 3)	5	+	ND	ND	ND	ND	ND

¹ ND = not done.

It may be mentioned that 14 of the cases recorded in Table 2, as well as one type 3 patient included in Table 3 (all of these patients are marked with an asterisk after the specimen number) were met with during the epidemiological study at a combined orphanage and nursery school in Stockholm where a paralytic case of poliomyelitis had just occurred. Repeated stool specimens were tested from 58 children at the institution. As will be presented in detail elsewhere (9,) 31 children were found to excrete poliovirus type 3. In six cases where the first specimen contained poliovirus a second stool specimen taken about 2-3 weeks later yielded adenovirus types 1 or 5. One of them again excreted poliovirus type 3 a week later. Another child had adenovirus type 5 in his first specimen and poliovirus type 3 three weeks later. Adenovirus types 1, 2, 3 or 5 were also recovered at one occasion or another from 8 children from whom no poliovirus was obtained. One of them was found to excrete adenovirus type 5 in the first specimen followed by type 1, one and two weeks later.

TABLE 3

Data on patients from whom adenovirus type 3 was isolated.

Strain No.	Age of patient (years)	Clinical diagnosis	Isolations of adenovirus type 3			Complement fixing antibodies against adenovirus		
			Stool	Naso-pharynx	Mesenteric lymph node	Serum 1	Serum 2	Serum 3
1675	11	Pharyngitis acuta	+	ND ¹	ND	< 2	8	ND
2561	6	Pharyngitis acuta + veg. adenoid.	+	ND	ND	ND	32	4
4636	5	Lymphadenitis mesenterii	+	ND	—	4	4	ND
4858	8	Lymphadenitis mesenterii	+	ND	—	8	32	ND
10335*	3.5	Pharyngitis acuta + lymphadenitis cervicalis	+	ND	ND	ND	ND	ND
10376	8	Scarlatina + sinusitis acuta + pharyngitis acuta + veg. adenoid.	+	ND	ND	< 2	32	ND
10387	2.5	Nasopharyngitis acuta + veg. adenoid.	+	ND	ND	< 2	8	ND
10551	4	Status post scarlatinam + angina tonsillaris streptococcica	+	ND	ND	ND	ND	ND
10553	8	Status post scarlatinam + angina tonsillaris streptococcica	+	ND	ND	ND	16	ND
10656	9	Scarlatina + conjunctivitis acuta	+	ND	ND	16	16	ND
XA 3	8	Pharyngitis acuta + veg. adenoid.	+	+	ND	< 2	16	ND
XA 13	5.5	Bronchopneumonia acuta + sinusitis acuta	+	+	ND	16	32	ND
XA 15	7.5	Nasopharyngitis acuta	+	+	ND	32	64	ND
XA 25	7	Nasopharyngitis acuta + sinusitis acuta	ND	+	ND	8	16	ND
XA 57	6	Nasopharyngitis acuta + conjunctivitis acuta	+	+	ND	32	128	ND
XA 78	8.5	Otitis med. ac. bil. + sinusitis acuta	+	+	ND	4	16	ND

¹ ND = not done.

Five stool specimens taken from another patient over a period of 6 weeks all contained type 5 virus. Unfortunately no sera were available from this study (except from patient 11810).

TABLE 4

Data on patients from whom adenovirus type 7 was isolated.

Strain No.	Age of patient (years)	Clinical diagnosis	Isolation of adenovirus type 7		Antibodies against adenovirus				Bacterial findings in nasopharynx
			Stool	Nasopharynx	Neutralizing (type 7)		Complement fixing		
					Serum 1	Serum 2	Serum 1	Serum 2	
9205	11	Nasopharyngitis acuta + lymphadenitis cervicalis + veg. adenoid	+	ND ¹	0	++	< 2	64	β -hemolysing streptococci
9215	8	Nasopharyngitis acuta + lymphadenitis cervicalis + veg. adenoid	+	ND	+++	+++	16	64	Haemophilus influenzae
9261	10	Meningitis asept. + angina tonsillaris + lymphadenitis cervicalis + veg. adenoid	+	ND	0	++	< 2	16	Negative
9267	12	Nasopharyngitis acuta + lymphadenitis cervicalis + sinuitis acuta	+	ND	0	++	< 2	64	Haemophilus influenzae
9269	8	Tonsillitis acuta + lymphadenitis cervicalis	+	ND	0	+++	< 2	16	Negative
9291	9	Angina tonsillaris	+	ND	0	++	< 2	8	Negative
9398	11	Sinuitis acuta + veg. adenoid	+	+	+	+++	8	64	Haemophilus influenzae
9434	6 ¹ / ₁₂	Nasopharyngitis acuta + bronchitis asthmatica + bronchopneumonia acuta	+	+	0	+++	< 2	32	Staphylococcus aureus
9787	5.5	Nasopharyngitis acuta + sinuitis acuta + bronchitis acuta + veg. adenoid	+	+	+	+++	8	64	Negative
9973	8	Angina tonsillaris + lymphadenitis cervicalis	+	ND	0	ND	4	ND	Negative
10334	11	Scarlatina + lymphadenitis cervicalis + veg. adenoid	+	ND	ND	ND	ND	ND	β -hemolysing streptococci
11090	6	Angina tonsillaris + lymphadenitis cervicalis + veg. adenoid (+ status post meningit. asept. post varicell.)	+	ND	0	++	< 2	256	Negative

Table 4 (continued)

Strain No.	Age of patient (years)	Clinical diagnosis	Isolation adenovirus type 7		Antibodies against adenovirus				Bacterial findings in nasopharynx
			Stool	Nasopharynx	Neutralizing (type 7)		Complement fixing		
					Serum 1	Serum 2	Serum 1	Serum 2	
12134	1.5	Nasopharyngitis acuta + otitis med. acuta + bronchopneumonia + pneumothorax spontanea	+	ND	++	++	64	32	Haemophilus influenzae
12136	1.5	Nasopharyngitis acuta + bronchitis acuta + conjunctivitis acuta	+	ND	+	+++	16	≥ 64	Staphylococcus aureus
12294	1.5	Bronchopneumonia acuta	+	ND	0	++	2	32	Haemophilus influenzae
12374	1	Nasopharyngitis acuta + laryngotracheitis acuta	+	ND	ND	+	< 2	16	Negative
XA 43	8	Nasopharyngitis acuta + sinusitis acuta + veg. adenoid	+	+	0	++	4	32	Negative

¹ ND = not done. Concerning the gradation of neutralizing antibodies see text.

Isolations of adenovirus type 3.—Type 3 virus has so far been the prevalent type isolated in Sweden. Most of the strains were recovered during the outbreaks, mentioned above, of pharyngoconjunctival fever in the fall of 1955. Thus 26 out of 28 stool specimens collected from persons in Kumla were found to contain type 3 virus. Two out of 26 patients were still positive two months later. Virus was also found in two different samples of sewage water collected in the epidemic region. The reasons for believing type 3 virus to be the cause of the epidemic will be discussed elsewhere (15). The frequency of various symptoms during this epidemic was similar to that reported by Bell and co-workers (2) with the exception that gastro-intestinal symptoms were common in our material.

Adenovirus type 3 was also recovered from 14 children at the Hospital for Infectious Diseases in Örebro who apparently suffered from a nosocomial infection, as well as from 7 contact cases (1). Fever, pharyngitis and conjunctivitis dominated the symptoms here too.

This type of virus was, furthermore, found in 16 scattered cases hospitalized in Stockholm. Some data about them are recorded in Table 3. The serological

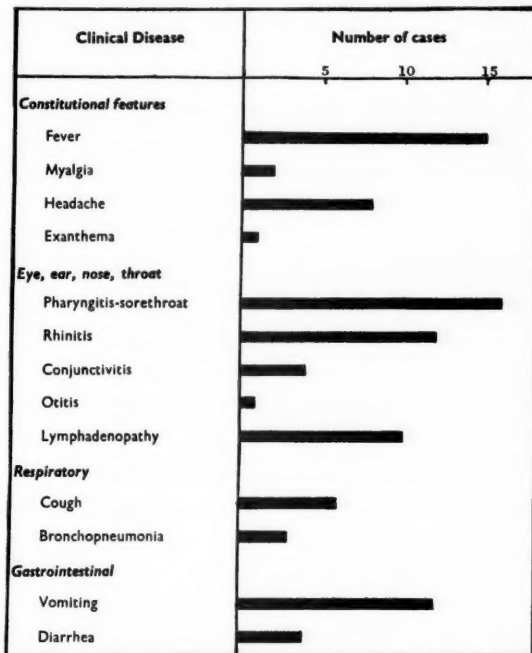


Fig. 1. Summary of clinical features of 17 patients from whom adenovirus type 7 was isolated.

data are in accordance with an acute infection with adenovirus. All patients were children and with the exception of the 2 cases with lymphadenitis mesenterii, all suffered from some form of upper respiratory disease. Pharyngitis was thus a common clinical finding whereas conjunctivitis was only observed in 4 cases.

Isolations of adenovirus type 7.—Adenovirus type 7 has been isolated from 17 children, age 8 months to 12 years, all of whom lived in a rather limited area of Stockholm. Thirteen of them were hospitalized during the fall of 1955, four during the following spring.

As seen in Table 4 all cases, at the time of virus isolation, showed a clinical picture which corresponds well with that reported in the studies of Berge and co-workers (3) and Dascomb *et al.* (4). The frequency of the more common symptoms and signs is presented in Figure 1. In 10 of the cases the onset of disease was acute, in the remaining more gradual. The most common clinical features presented by the patients were fever, pharyngitis and rhinitis. The fever lasted for 5 to 10 days with a maximum ranging from 39.6–40.7°C.

X-ray examination of the chest was performed in 13 of the cases. Bronchopneumonia was disclosed in three patients. In 10 cases X-ray examination of the accessory sinuses was carried out. Seven of them showed signs of sinusitis. Eight out of 9 patients examined by X-ray were found to have adenoids.

The stool specimens as well as the four throat swabs were collected 2-9 days after onset of the acute symptoms. The serological data, especially the rises in neutralizing and/or CF antibodies in 14 out of 15 cases investigated, indicate that the infections with type 7 virus occurred simultaneously with the acute symptoms of disease.

As revealed in Table 4 nasopharyngeal swabs were also sent for bacteriological examination. Eight of them came out negative. From six *Haemophilus influenzae* was recovered, from two β -hemolysing streptococci, and in two instances *staphylococcus aureus* was found (G. Tunevall, personal communication). The picture is thus complicated by the fact that several potential pathogens were prevalent among the children of this area at the time the type 7 strains were recovered. Again, it is difficult to draw any definite conclusions regarding the consequences of the adenovirus infections.

Summary

The recovery of 148 strains of adenovirus belonging to 6 different types is described. Type 3 dominates the material and was mostly found in connection with an upper respiratory disease such as pharyngoconjunctival fever. Type 7 was isolated from children with a basic syndrome of fever, pharyngitis and rhinitis. Upper respiratory infections dominate also among the cases from whom adenoviruses of types 1, 2 or 5 were isolated. Adenoviruses types 2, 3 or 5 have been found in the stools of six out of 82 cases suffering from lymphadenitis mesenterii. In three cases the virus was also recovered from mesenteric lymph nodes. Only one out of the 148 strains could not be referred to any of types 1-7, 9 or 10. The difficulties in drawing etiological conclusions in many of the cases are discussed. Valid criteria were probably fulfilled only in the study of a type 3 outbreak.

Sur l'existence des types différents d'adenovirus en Suède.

L'auteur décrit le cultivation de 148 souches d'adenovirus appartenant à 6 types différents. Le type 3 domine le matériel et a été trouvé principalement en liaison avec un trouble des voies respiratoires supérieures tel que la fièvre pharyngoconjonctivale. Le type 7 a été isolé sur des enfants présentant un syndrome basique de fièvre, pharyngite et rhinite. Les infections des voies respiratoires supérieures dominent dans les cas dans lesquels on a isolé les adenovirus des types 1, 2 ou 5. Les adenovirus des types 2, 3 ou 5 ont été trouvés dans les selles de 6 sujets sur 82 souffrant d'une lymphadenite mesenterique. Dans 3 cas le virus a été obtenu dans les glandes lymphatiques du mésentère. L'une seulement des 148 souches n'a pu être rapportée à l'un des types 1-7, 9 ou 10. L'auteur discute les difficultés qu'il y a à tirer des conclusions étiologiques

dans beaucoup de cas. Des critères valables n'ont probablement été réunis que dans une épidémie du type 3.

Über das Vorkommen von verschiedenen Typen Adenovirus in Schweden.

Es wird die Züchtung von 148 Stämmen von Adenovirus, die 6 verschiedenen Typen gehören, beschrieben. Typ 3 beherrscht das Material und wurde meist in Verbindung mit einer Krankheit der oberen Luftwege, wie pharyngokonjunktivales Fieber, gefunden. Der Typ 7 wurde von Kindern mit einem Grundsyndrom von Fieber, Pharyngitis und Rhinitis isoliert. Die Infektionen der oberen Luftwege überwiegen also unter den Fällen, von denen Adenovirus der Typen 1, 2 und 5 isoliert wurden. Die Adenovirustypen 2, 3 und 5 wurden in den Stühlen von sechs von 82 Fällen, die an Mesenteriallymphadenitis litten, gefunden. In drei Fällen wurde das Virus auch von Mesenteriallymphknoten gewonnen. Nur einer der 148 Stämme konnte nicht einer der Typen 1-7, 9 oder 10 zugeschrieben werden. Die Schwierigkeiten, die bestehen, um in vielen der Fälle ätiologische Schlüsse zu ziehen, werden diskutiert. Ein gültiges Kriterium konnte wahrscheinlich nur beim Studium der Epidemie des Typs 3 gewonnen werden.

Sobre la existencia de diferentes tipos de adenovirus en Suecia.

Se describe el cultivo de 148 cepas de adenovirus pertenecientes a 6 diferentes tipos. El tipo 3 domina el material y se ha encontrado la mayoría de las veces en conexión con una enfermedad del aparato respiratorio como fiebre faringoconjuntival. El tipo 7 fué aislado de niños con un síndrome básico de fiebre, faringitis y rinitis. Por lo tanto dominaron las enfermedades del aparato respiratorio entre los casos de los cuales se aislaron adenovirus de los tipos 1, 2 o 5. Los tipos de adenovirus 2, 3 y 5 se han encontrado entre las evacuaciones de 6 de 82 casos de linfadenitis mesentérica. En tres casos el virus ha podido encontrarse también en los nódulos linfáticos mesenteriales. Solamente una de las 148 cepas no ha podido someterse a ninguno de los tipos 1-7, 9 o 10. Se discute la dificultad de sacar conclusiones etiológicas en muchos de los casos. Un criterio válido solamente se ha podido ganar en el estudio de la epidemia del tipo 3.

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The *in vitro* Glucose Uptake Inhibiting Effect of Body Fluids in Infantile Toxicosis

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In recent years the rat diaphragm test (4, 9, 10, 12, 13, 15) has gained acceptance in studies on certain biochemical, physiological and clinical problems. The essential features of the procedure are that rat diaphragm is incubated in the Warburg apparatus and is subsequently tested quantitatively for sugar uptake, glycogen content, gas exchange, etc. The sensitivity and reliability of the method made it possible to elucidate *in vitro* the metabolism of a variety of substrates, as well as the site of action and mode of action of hormones. By strictly adhering to certain principles, Vallance-Owen and Hurlock have improved the method and made it suitable for the quantitative estimation of insulin in serum. These authors showed that in normal sera the sugar uptake is increased on fasting, because the serum contains free (or as they put it: "effective") insulin.

We have carried out similar estimations in sera and cerebrospinal fluid from infants suffering from toxicosis. It was assumed that the data thus obtained would sensitively indicate the possible presence of factors of humoral nature acting on cell metabolism in body fluids during toxicosis, and if such factors can actually be demonstrated, their stimulating or inhibitory nature would also be determinable. Thus, the investigations described in this paper were intended to contribute information to the problems of the disturbance of carbohydrate metabolism associated with infantile toxicosis.

Materials and Methods

Apart from slight, insignificant modifications, the method employed was that described by Vallance-Owen and Hurlock (14). Young Wistar strain rats, weighing 120 to 180 g were fasted for 24 hours prior to the experiment. After killing the animals by decapitation, the diaphragm was exposed without delay, cut with scissors carefully along the insertion line and the pars membranacea was removed. The anterior $\frac{2}{3}$ of the bilateral hemidiaphragms were used. These were placed into chilled Krebs-Ringer-bicarbonate solution, which had been prepared in advance. The diaphragm was

dried with filter paper at 15 minutes and transferred by means of tweezers into an adequately prepared Warburg dish. Into the dishes were measured Krebs-Ringer-bicarbonate solution, or serum, or CSF, each in a volume of 1.5 ml. Previously, the glucose concentration of these test fluids had been adjusted to 300 mg per cent, by adding sufficient volumes from a 3 per cent dextrose stock solution. The 2 hemidiaphragms from the same animal were placed simultaneously into the Warburg dish. The dishes were then exposed to the usual 5 per cent CO_2 95 per cent O_2 gas flow for 5 minutes, which was followed by incubation for 90 minutes in a 38°C water bath, shaking at a rate of 90 to 100/min. The solids in the diaphragms were estimated after incubation, by drying at 105°C until constant weight was reached. The Somogyi method (11) for the estimation of sugar was employed. Each specimen was tested for sugar content both prior to and after incubation. Sugar consumption in mg has been calculated for 90 minutes and 1 g dry weight diaphragm.

Material

Normal sera were obtained by venipuncture from infants and children, convalescent or showing no symptoms. The fasting serum was taken prior to the morning meal, tolerance serum was obtained $1\frac{1}{2}$ hours after the ingestion of 1.75 g/kg dextrose.

Normal CSF was obtained from fasting, symptom-free patients.

The patients with toxicosis tested were uniform only in that they all showed the cardinal symptoms and signs of toxicosis, notably fever, gastrointestinal symptoms, grave shock with central and peripheral circulatory failure, loss of consciousness, superficial ("high") breathing, oliguria, etc. Marked dehydration occurred in a few cases only. However, various, often unidentified infections were in the background of the above grave clinical picture. In order to facilitate a better evaluation of single results, it has been deemed essential to present a brief characterisation of each case and to point out the time at which blood or CSF was taken in single cases.

Case 1.—Ny. M., aged 6 months was admitted with dyspepsia coli enteritis. The extreme dehydration and grave toxicosis found on admission improved slightly on infusions, but the patient suddenly died with the symptoms of dehydration toxicosis on the 10th day of hospital treatment. Blood was obtained by heart puncture immediately after death. The serum showed the following values: total base 186 mEq/l, Na 167 mEq/l, NPN 70 mg per cent, sugar 495 mg per cent.

Case 2.—J. G., aged 3 months, suffering from dysenteric toxicosis, developed severe dehydration and circulatory failure during the last days of the 2-week hospital treatment. In that period the infant lost 1000 g weight, in spite of the administration of infusions. Blood was taken immediately after death, by heart puncture. Blood serum values: total base 151 mEq/l, Na 134 mEq/l, NPN 86 mg per cent, blood sugar 526 mg per cent.

Case 3.—I. J., 8 months old, had purulent meningococcal meningitis, could not be fed, vomited often and developed a severe circulatory failure during the few days preceding death. Immediately after the child died, blood was obtained by heart puncture. NPN: 74 mg per cent, blood sugar 385 mg per cent.

Case 4.—W. J., aged 8 months, had developed a fudroyant toxicosis with hyperpyrexia after 5 days of uneventful whooping cough, with coffee ground vomitus, convulsions, grave impairment of consciousness and circulatory failure and died within 10 hours from the onset of acute symptoms. CSF was obtained by lumbar puncture 3 hours after the onset of acute symptoms, at the time convulsions developed.

Blood was obtained by heart puncture immediately after death. Serum values: total base 171 mEq/l, Na 160 mEq/l, sugar 13 mg per cent, NPN 134 mg per cent, NPN in CSF 62 mg per cent, sugar in CSF 110 mg per cent.

Case 5.—T. M., aged 8 months, developed grave septic-toxic disease with loss of consciousness, high fever, unfeedability, ileus-like symptoms in the course of a bilateral purulent otitis and bronchopneumonia. Antibiotics infusions, heart stimulants were ineffective and the baby died after 3 days of treatment. Immediately after death blood was obtained by heart puncture. Blood sugar was 20 mg per cent.

Case 6.—P. E., aged 9 months, was admitted with whooping cough of 2 weeks duration and fever. After losing 600 g weight because of vomiting of extreme intensity, the baby developed intractable convulsions, loss of consciousness, circulatory failure and died in about 12 hours after the onset of acute symptoms. Blood was obtained immediately after death by heart puncture. Blood sugar was 44 mg per cent.

Case 7.—P. J., aged 10 months, developed morbilli 3 days, and orthopnea 1 day before admission. On admission the infant was unconscious, circulatory failure, fever (42°C) and high breathing were noted. CSF was obtained by lumbar puncture 3 hours before death, blood from the longitudinal sinus 1 hour later. Serum values: total base 171 mEq/l, Na 160 mEq/l, sugar 63 mg per cent. CSF values: total base 160 mEq/l, Na 158 mEq/l, sugar 146 mg per cent.

Case 8.—S. A., aged 7 months, developed fudroyant hyperpyretic toxiosis. On admission bronchopneumonia was found. One day later hyperpyrexia, convulsions, loss of consciousness and grave circulatory failure developed and the infant died in 8 hours. Blood was obtained 2 hours before death. Serum values: total base 161 mEq/l, Na 148 mEq/l, sugar 0 mg per cent.

Case 9.—S. A., aged 5 months, developed suddenly high fever, high respiration, disturbance of consciousness, and circulatory failure on the day of admission. Death ensued four hours after admission. Lumbar puncture and blood sampling were carried out immediately after admission. Serum values: total base 165 mEq/l, Na 151 mEq/l. In CSF: total base 171 mEq/l, Na 162 mEq/l, sugar 130 mg per cent.

Case 10.—F. N., aged 4 months, had grave dehydration toxiosis and gastroenteritis. The stool was positive for dyspepsia coli 111. Continuous intravenous drip infusion resulted in some improvement, but had to be discontinued after a few hours because of technical difficulties. Shortly after that the infant's condition deteriorated. Blood was obtained at that time and the following values were found. Serum total base 158 mEq/l, Na 148 mEq/l, K 3.2 mEq/l, blood sugar 38 mg per cent. Infusion treatment was then continued and the baby recovered, after prolonged reparation.

Case 11.—Cs. Sz., aged 10 months, was found to suffer from extensive bronchopneumonia on admission, associated with increasing circulatory failure. On admission comatous state, grave intestinal passage impairment, dyspnea and circulatory failure were found, and CSF was obtained by lumbar puncture. The baby died 12 hours after admission.

Results

In order to test the efficiency and reliability of the method, the right and left hemidiaphragms from the same animal were incubated simultaneously in the Krebs-Ringer-bicarbonate buffer. The results of these tests are shown in Table 1. It can be seen, that although the diaphragms from single animals may vary considerably in sugar consumption, as calculated for

TABLE 1

The glucose uptake of the unilateral hemidiaphragm of a rat, as related to that of the contralateral hemidiaphragm from the same animal, after incubation in Krebs-Ringer, calculated as mg glucose / 1 g dry weight, 1½ hours.

No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Right side	37	45	45	60	61	65	25	32	43	41	38	33	37
Left side	33	49	42	62	59	67	23	31	45	42	40	32	35

TABLE 2

The glucose uptake from normal fasting serum, as related to that from Krebs-Ringer, calculated as mg glucose / 1½ hours / 1 g dry weight.

No.	1	2	3	4	5	6
Krebs-Ringer	31	47	42	30	40	35
Fasting serum	37	52	46	45	47	37

90 minutes and 1 g dry weight, the glucose uptake of the bilateral hemidiaphragms from the same animal shows essentially identical values.

Glucose uptake in normal sera and CSF was estimated in a total of 16 cases. The sugar uptake from body fluids was compared with the sugar consumption of the contralateral hemidiaphragm in Krebs-Ringer. The values obtained for 6 normal fasting sera are presented in Table 2. It can be seen that, as related to the hemidiaphragms incubated in Krebs-Ringer, the hemidiaphragms incubated in normal fasting sera took up more sugar. The data in Table 3 reveal that sugar uptake was still higher in case the diaphragms had been incubated in sera from normal children previously given tolerance doses of glucose. In Table 4 are shown the values for glucose uptake from normal cerebrospinal fluids. The glucose uptake from the 4 CSF's tested was closely similar to that obtained after incubation in Krebs-Ringer.

The glucose uptakes from sera of children with toxicosis are shown in Table 5, and those from the toxicosis cerebrospinal fluids in Table 6. It is obvious from these tables that the glucose uptake of the diaphragms from the body fluids taken from patients with toxicosis was invariably highly inhibited.

Statistical analysis of the results has revealed that, according to the calculations, the sugar uptake by the hemidiaphragm significantly increased in the normal fasting sera and in the sera taken after the administration of tolerance doses of glucose. In contrast with this, glucose uptake was

TABLE 3

The glucose uptake from normal sera 1½ hours after glucose tolerance with 1.75 g/kg glucose, as compared to that from Krebs-Ringer, calculated as mg glucose / 1½ hours / 1 g dry weight.

No.	1	2	3	4	5	6
Krebs-Ringer	38	33	32	24	52	43
Tolerance serum	42	37	44	48	58	49

TABLE 4

The glucose uptake from normal CSF, as compared to that from Krebs-Ringer calculated as mg glucose / 1½ hours / 1 g dry weight.

No.	1	2	3	4
Krebs-Ringer	48	46	46	37
Normal CSF	53	40	39	36

TABLE 5

The glucose uptake from sera obtained from infants with toxicosis, as compared to that from Krebs-Ringer, calculated as mg glucose / 1½ hours / 1 g dry weight.

No. of cases	1	2	3	4	5	6	7	8	9	10
Krebs-Ringer	39	63	65	31	50	69	43	49	45	41
Toxic serum	21	23	24	19	16	29	25	30	25	15

TABLE 6

The glucose uptake from CSF obtained from infants with toxicosis, as compared to that from Krebs-Ringer, calculated as mg glucose / 1½ hours / 1 g dry weight.

Case no.	4	7	9	11
Krebs-Ringer	40	33	49	42
Toxic CSF	22	16	27	19

highly significantly diminished in sera from cases of infantile toxicosis, in the samples taken during life and after death alike. The sugar uptake from normal CSF did not (as far as one can judge from the relatively small number of cases) differ from that from Krebs-Ringer, while in the toxic CSF the sugar consumption was significantly lower than normal.

Discussion

Our experiments have shown that *in vitro* the glucose uptake from body fluids obtained from infants with toxicosis is inhibited. It is obvious that a wide variety of factors and agents may be responsible for such an inhibition of glucose uptake.

1. It is proved that sugar uptake is significantly influenced by the *experimental conditions*, including temperature, composition of the gas mixture, the rate at which the incubated material is shaken, etc. (10). The method we have employed eliminates these factors, since the sugar uptake was invariably compared with that by the contralateral hemidiaphragm from Krebs-Ringer solution. Another factor profoundly influencing glucose uptake is the concentration of glucose in the medium (5). In our experiments the initial concentration of glucose in the medium was adjusted to 300 mg per cent in every case. The two dishes were exposed to the same gas flow and were incubated together. Effects modifying glucose uptake as result from changes in pH and ionic composition (10) could be less effectively eliminated. However, the measured alkali reserve was not always low, and the ionic pattern showed no uniform changes of significance: these facts make it unlikely that the modifying effect on glucose uptake can be traced back to the latter factors.

2. Insulin is the only hormone among the hormones acting on carbohydrate metabolism (as far as it is known today) that is capable of lowering blood sugar level. The high number of the *insulin-antagonist* hormones offers various possibilities that the stimulating action of insulin on the sugar uptake by cells be abolished, or inhibition may develop (2). It has been known for a long time that in toxicosis the sensitivity to insulin is diminished and increased to adrenalin, the blood sugar curves being higher and protracted. On grounds of clinical observation made on the adrenergic preponderance Gegesi Kiss (3) showed that the administration of adrenalin had noxious sequelae. Kovács *et al.* (9) have shown it for traumatic shock, which has so many features in common with infantile dehydration toxicosis (Kerpel-Fronius (7)) that the sugar uptake of the diaphragms from rats in shock was inhibited and this effect could be prevented by hypophysectomy and adrenalectomy. Wiggers and associates (16), when reporting on the favourable action of Dibenamine, a well-known sympathicolytic agent, supplied decisive corroborative evidence to the view that the preponderance of the sympathetic tone is in the axis of the pathogenesis of shock.

3. It is likely that the *in vitro* uptake of glucose is determined not only by the quantitative relations of different hormones, but the *metabolites potentiating or inactivating hormones* are also involved in the effect. It is

known that in the presence of free SH groups insulin loses its activity. The insulin effect can be neutralised in the presence of m/50 cysteine and m/45 glutathion (6). It is remarkable that at the same time these agents can potentiate the effect of adrenalin (8). It seems that these agents play significant roles in physiological hormonal activities. In the metabolic processes involved in toxicosis the possibility is given that biologically active metabolites be produced and accumulated in the body fluids. We are going to publish data (1) which justify the view that in infantile toxicosis the humoral equilibrium of the system is upset by the action of pathological metabolites, which act also on the energy metabolism of cells and, through the latter, on the water and electrolyte content of the intracellular space.

Ultimately, the rat diaphragm test, in which a strong inhibition of glucose uptake from body fluids was demonstrated, does not decide which factors are responsible for this effect. It is certain, however, that *in the body fluids representing the internal milieu for the cells there are effects which induce grave, and eventually irreversible, changes in cell metabolism.*

Summary

The action of body fluids from normal infants and infants with toxicosis on the glucose uptake has been studied by the rat diaphragm test.

1. The diaphragms incubated in normal fasting sera and in sera taken after the administration of tolerance doses of glucose consumed more glucose than those incubated in Krebs-Ringer.

2. No increase in glucose uptake has been observed after incubation in normal CSF.

3. The glucose uptake of diaphragms incubated in body fluids (serum or CSF) from infants with toxicosis has been found to be highly inhibited in every case.

Absorption du glucose in vitro. L'action inhibitrice des liquides organiques dans la toxicose infantile.

L'action des liquides organiques d'enfants normaux et d'enfants atteints de toxicose sur l'absorption du glucose a été étudiée au moyen du test sur le diaphragme du rat. —

1) Le diaphragme incubé dans des sérums normaux et dans des sérums recueillis après l'administration d'une dose de tolérance de glucose absorbe plus de glucose que ceux incubés dans du Krebs-Ringer. — 2) Il n'a pas été observé d'augmentation de l'absorption du glucose après incubation en liquide céphalo-rachidien normal. — 3) L'absorption de glucose par des diaphragmes incubés dans des liquides organiques (serum ou liquide céphalo-rachidien) d'enfants ayant une toxicose s'est révélé hautement inhibée dans tous les cas.

Der Glukoseaufnahme hemmende Effekt der Körperflüssigkeiten bei infantiler Toxikose in vitro.

Die Wirkung der Körperflüssigkeiten normaler Kinder sowie von Kindern mit Toxikose auf die Glukoseaufnahme ist mittels der Rattenzwerchfellprobe untersucht worden. 1) Die in normalen Nüchternsera sowie in nach erfolgter Verabreichung von

Glukose in Toleranzdosen abgenommenen Sera inkubierten Zwerchfelle nahmen mehr Glukose auf als die in Krebs-Ringer inkubierten. 2) Es ist nach Inkubierung in normalen Liquor keine Steigerung der Glukoseaufnahme festgestellt worden. 3) Es zeigte sich, dass die Glukoseaufnahme von in Körperflüssigkeiten (Serum oder Liquor) von Kindern mit Toxikose inkubierten Zwerchfellen in jedem der Fälle wesentlich gehemmt war.

Inhibición en la toxicosis infantil del efecto de los líquidos orgánicos por el ingreso de glucosa in vitro.

La acción de los líquidos orgánicos provenientes de niños normales y de niños con toxicosis en la glucosa ingresada, ha sido estudiada mediante la prueba del diafragma de ratón. 1. Los diafragmas incubados en sueros normales ayunados y en sueros tomados después de la administración de dosis de tolerancia de glucosa, consumieron más glucosa que los incubados en Krebs-Ringer. — 2. No se ha observado incremento del ingreso de glucosa después de la incubación en el líquido encefalorraquídeo normal. — 3. El ingreso de glucosa por los diafragmas incubados en los líquidos orgánicos (suero o líquido encefalorraquídeo) de niños con toxicosis, se ha comprobado estaba altamente inhibido en cada caso.

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Cirrhosis of the Liver in Two Children with Hyperproteinaemia

by JENS BERGSTEDT and CHRISTIAN LINGEN

In our two patients, electrophoresis showed a strange serum protein pattern, with concomitant hyperproteinaemia indicating the presence of multiple myeloma, whereas histopathologic examination disclosed cirrhosis of the liver.

One of the characteristic features in certain cases of multiple myeloma is a marked increase in the gamma globulin fraction, which may be of a true protein or of a paraprotein nature. It is expressed as a sharp peak in the electrophoretic diagram, a decrease in the alpha globulin fraction, and hyperproteinaemia (2, 5). These features were present in our patients, and initially led us to suspect the existence of multiple myeloma (cf. Fig. 4). For this reason, repeated roentgenologic examinations and sternal punctures were made, as well as tests for Bence-Jones protein. The results were consistently negative. Further clinical investigations indicated some form of liver damage instead.

As far as the electrophoretic pattern in liver damage is concerned, cirrhosis of the liver, for example, is characterized by a decrease in the albumin fraction, often normal alpha and beta globulin, and a considerable increase in gamma globulin, expressed as a broad-based, rounded peak (1, 3, 4, 5, 6, 7). Hyperproteinaemia has not earlier been observed in cirrhosis of the liver in children (3, 6, 8). We verified this fact by a study of the total serum protein values in patients treated at Kronprinsessan Lovisas Barnsjukhus from 1936 to 1955 inclusively, under the diagnosis of cirrhosis of the liver. In the majority of cases, the diagnosis was based on histopathologic examination.

An account of our two cases follows.

Case Reports

Case 1, a 10-year-old girl. She had previously been healthy. There was no history of umbilical infection, nor of jaundice. She was admitted to hospital on April 4, 1952 and was hospitalized for altogether 3 months on several occasions up to December

TABLE 1

Case 1. Electrophoresis according to Antweiler and paper electrophoresis.

Antweiler electrophoresis: albumin to globulin ratio 0.75. Total serum protein (maximum value) 11.5 g/100 ml.

Fraction %	Electrophoresis Antweiler	Paper electrophoresis
Albumin	38.2	35.1
Alpha globulin	4.8	4.4
Beta globulin	10.9	11.0
Gamma globulin	46.1	49.5

1952, and was followed up to 1956. She was admitted the first time on account of acute swelling of the right wrist. Examination then showed enlargement of the liver, whereas the spleen was not palpable (confirmed by a scout film of the abdomen). S.R.: 64 mm/hr; for other laboratory data, see Table 3.

After a few weeks' bed rest, the S.R. returned to normal, and the swelling of the right wrist subsided. The spleen had instead become pathologically enlarged. On the first admission, the blood counts were normal, but after about 6 months, anaemia, leukopenia and thrombocytopenia appeared. Repeated sternal punctures disclosed nothing abnormal. Roentgenologic examination of the oesophagus showed no varices.

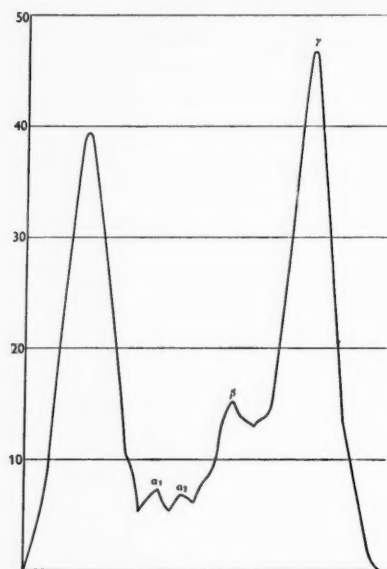


Fig. 1. Electrophoretic curve in Case 1. Note the narrow, high gamma globulin peak. Values in per cent.

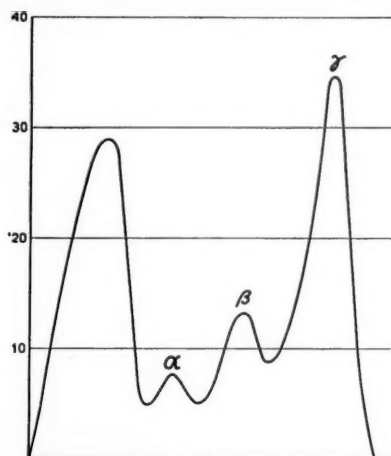


Fig. 2. Electrophoretic curve in Case 2. Note the same gamma globulin peak. Values in per cent.

In view of the difficulty in interpreting the clinical picture, and of the presence of hyperproteinaemia, fractionated analysis of the serum protein was made (Table 1). A markedly pathologic electrophoretic pattern was obtained, with greatly increased gamma globulin, expressed as a narrow, high peak (Fig. 1). Multiple myeloma was therefore suspected, but could not be confirmed. In the course of 6 months, repeated roentgenologic examinations of the skeleton were made, as well as sternal puncture and tests for Bence-Jones protein, all with negative results.

Because of the negative attitude of the parents, laparotomy with a view to confirming the clinical suspicion of liver disease was not performed for 8 months (Dec. 1952). Operation showed a small-noduled, enlarged liver and an enlarged spleen. Histopathologic examination (Prof. H. Bergstrand) disclosed a late stage of acute hepatitis in the form of chronic yellow atrophy of the liver, but no fatty infiltration or iron pigment.

TABLE 2

Case 2. Electrophoresis according to Antweiler and paper electrophoresis.

Antweiler electrophoresis: albumin to globulin ratio 0.79. Total serum protein (maximum value) 10.0 g/100 ml.

Fraction %	Electrophoresis Antweiler	Paper electro- phoresis
Albumin	44.4	30.0
Alpha globulin	8.0	9.0
Beta globulin	14.9	14.0
Gamma globulin	32.7	47.0

TABLE 3

Laboratory data in Cases 1 and 2.

	Case 1 April 1952	Nov. 1952	May 1954 (outpat.)	Aug. 1955	Case 2 July 1952	March 1953	Feb. 1955
Haemoglobin	81 %	76 %	86 %	68 %	80 %	77 %	
R.B.C.	4,000,000	3,900,000	4,400,000	3,200,000	4,200,000	4,000,000	
W.B.C.	5,000	2,000	3,000	2,600	5,000	5,000	
Urinary urobilin (Schlesinger)	neg.	neg.	neg.		+++	+++	
Thymol turbidity	17 units	38 units		19 units	35 units	40 units	
Icterus index (Meulengracht)	1:11	1:22		1:20	1:60	1:60	1:35
Prothrombin index	77	78			100	79	
Serum cholesterol					300 mg/ 100 ml	167 mg/ 100 ml	
S.R./1 hr	30 mm	20 mm	17 mm		40 mm	80 mm	70 mm
Bence-Jones protein	neg.	neg.	neg.		neg.	neg.	
Total serum lipids		560 mg/ 100 ml				783 mg/ 100 ml	
Bromsulphthalein test		0 ret.		59 %			
Galactose tolerance		1.53 g					
Thrombocytes	200,000	76,000	80,000	74,000			
Total serum protein, g %	11.5	9.4	7.3	7.2	10.6	10.4	10.4
Albumin %	45.2	35.1	40.5	28.2	35.5	33.5	36.0
α_1 -globulin	2.7	2.1	4.4	9.2	4.3	7.0	
α_2 -globulin		4.4	4.6	8.7	6.1		
β -globulin	7.0	11.0	12.3	8.7	13.2	8.4	15.0
γ -globulin	44.1	49.5	40.5	50.0	42.1	47.7	42.0

The patient was subsequently asymptomatic until December 1955, when she was readmitted to hospital with haematemesis. The liver was then palpable at the level of the costal margin, and the spleen in the umbilical plane; ascites was also present. Roentgenologic examination showed portal hypertension and oesophageal varices. There was severe anaemia, leukopenia and thrombocytopenia, as well as hypoproteinaemia. Electrophoresis showed the gamma globulin to be 42 per cent. After blood transfusions, a spleno-renal shunt was performed in March 1956. On this occasion as well, the liver was found to be small-noduled.

Case 2, a 12-year-old boy. He had previously been healthy. He fell ill in October 1951 with jaundice, dark-coloured urine and pain in the right side of the abdomen. Icterus index (Meulengracht) 1:64. He was treated at a provincial hospital until July

1952, his condition remaining unchanged. He was admitted to Kronprinsessan Lovisas Barnsjukhus in July 1952 and was hospitalized for several periods until March 1953. On admission, there was severe jaundice; the liver was greatly enlarged but not the spleen (confirmed by scout film of the abdomen). For laboratory data, see Table 3. Like the preceding case, this patient had hyperproteinaemia (maximally 10 per cent) and a pathologic electrophoresis curve (Fig. 2), with greatly increased gamma globulin, expressed as a narrow, high peak on the diagram, cf. Table 2). Laparotomy was performed. The histopathologic examination (Prof. H. Bergstrand) showed chronic hepatitis in the form of yellow atrophy with marked fatty infiltration of the liver cells. Cholangiography was performed concurrently with laparotomy, and showed normal conditions.

Follow-up examination in March 1955. There was subjective improvement; the patient was able to be up but did not attend school. He was jaundiced, and numerous vascular "spiders" were visible. The liver was palpable at the costal margin, and the spleen four fingerbreadths below the costal margin in the mammillary line. The earlier hyperproteinaemia persisted, the total serum protein being 10.4 per cent, whereas the narrow, high gamma globulin peak on the electrophoretic diagram was replaced by an equally high peak with a broad base.

Summary

A description is given of two cases of cirrhosis of the liver combined with hyperproteinaemia and an electrophoretic pattern indicative of multiple myeloma. The diagnosis was established at histopathologic examination. X-ray of the skeleton was negative. The increase in total serum protein is pointed out as a feature of great interest; it is generally present in multiple myeloma, but as far as we have been able to ascertain, has not been observed in cirrhosis of the liver in children.

Cirrhose du foie chez deux enfants ayant de l'hyperprotéïnémie.

Rapport de deux cas de cirrhose du foie combinée avec de l'hyperprotéïnémie et un type électrophorétique indicateur de myélomes multiples. Le diagnostic fut posé sur la base d'un examen histopathologique. Le squelette n'avait montré aucune anomalie aux rayons X. L'augmentation du total de sérum-protéine est considérée comme un aspect de grand intérêt; cette augmentation s'observe généralement en cas de myélomes multiples, mais, pour autant qu'on le sache, elle n'avait pas encore été observée dans la cirrhose du foie chez d'enfants.

Lebercirrhose bei zwei Kindern mit Hyperproteinämie.

Beschreibung von zwei Fällen von Lebercirrhose, die mit Hyperproteinämie und einem elektrophoretischen, multiple Myeloma ähnlichen Muster einhergingen. Die Diagnose wurde auf Grund einer histopathologischen Untersuchung gestellt. Die Röntgenaufnahmen des Skelettes waren negativ. Die Steigerung des Gesamtserumproteins wird als ein sehr wichtiges Kennzeichen bezeichnet; obwohl sie bei multiple Myeloma gewöhnlich auftritt, ist sie, soweit sich feststellen lässt, bei Kindern, die an Lebercirrhose litten, nicht beobachtet worden.

Cirrosis del hígado en dos niños afectos de hiperproteinemia.

Se relatan dos casos de cirrosis hepática acompañada con hiperproteinemia y cuadro electroforético indicando mieloma múltiple. El diagnóstico fué establecido a raíz del examen histopatológico. La radiodiagnosis del esqueleto fué negativa. El aumento total de seroproteína se señala como un hecho de gran interés; existe generalmente en el mieloma múltiple, pero por más que haya podido compararse, no se ha observado en la cirrosis hepática infantil.

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Gastric Hemorrhagic Telangiectasia in a Child

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and B. IVEMARK

The hereditary hemorrhagic telangiectasia, the Rendu-Osler-Weber disease, has been discussed in several papers. It is characterized by multiple telangiectases in the skin and mucous membranes, recurrent bleedings from these lesions and a family history. In a later stage liver damage may occur (Fitz-Hugh, 1931; Johnson & Nordenson, 1942). The vast majority of cases described has been adults, the changes not apparent until the second decade or later. The telangiectases are pin-point or sometimes spider-like and may be found in any organ of the body. There are no abnormalities in blood clotting nor in other blood tests. Usually, however, a secondary anemia develops as a result of the bleedings. Epistaxis has been the predominant symptom.

Gastrointestinal hemorrhage caused by telangiectases is uncommon, in particular bleeding from the stomach. Among 31 cases of hereditary hemorrhagic telangiectasia treated at the Mayo Clinic during 1920-1944 there were no cases of gastrointestinal hemorrhage (Gambill, 1946). Several members of the large kindred studied by Dolowitz (1953) died following "internal bleeding, cerebral, pulmonary, gastrointestinal". The study gives no figures of the frequency of the gastrointestinal bleedings, nor was the presence of gastrointestinal telangiectases proved. A number of other adult cases with hematemesis or melena have been published. Williams & Brick (1955) gave an extensive review of 42 published cases. In about one half of these there was no proof of telangiectases in the gastrointestinal tract and the diagnosis was made by exclusion.

The series published by Hurst & Plummer (1932) included a 19-month-old child with hematemesis and melena. SNYDER & DOAN (1944) described a girl, who died at an age of 10 weeks from gastrointestinal bleeding and hematuria, caused by telangiectases. Autopsy showed lesions in the skin, mucous membranes, lungs, spleen, liver, intestines, kidneys and the brain.

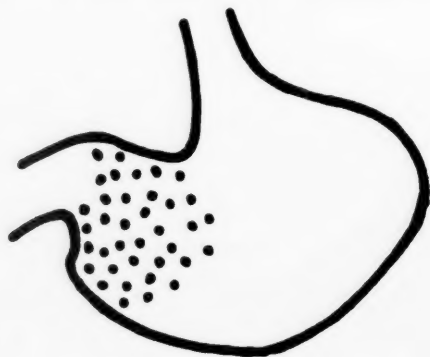


Fig. 1. Schematic drawing of the gastroscopic view.

Case History

This report deals with a 5-year-old boy with capillary telangiectases in the skin (face, trunk, left arm and both legs) since birth. No similar lesions and no suspected instances of epistaxis or other bleedings had occurred in other members of the family. During the first two years of life he had recurrent epistaxis. At the age of 3 years he developed recurrent hematemeses and melena with intervals of 3–5 months, necessitating repeated admission to hospital and blood transfusions. During the attacks hemoglobin averaged 30–50 per cent and erythrocytes 1.5–3 millions. He was admitted to the Pediatric Clinic at Karolinska Sjukhuset in Nov. 1954 at the age of 4 years. Blood tests including blood clotting were normal, hemoglobin 80 per cent (11 g %), erythrocytes 3.7 mill. Mucous membranes in nose and mouth were normal. Liver and spleen were not enlarged. Roentgenologic examination of the stomach showed large mucous folds; colon was normal. Rectosigmoidoscopy normal, no telangiectases.

Gastroscopy (Ihre): Oesophagus, cardia, fornix and corpus of the stomach were all normal. In the distal third (antrum and canal) a network of dilated vessels were seen in a pale, thick mucous membrane. The upper limit of the lesions was not distinct (Fig. 1).

Because of the recurrent hemorrhages from the stomach and in spite of the possibility of further telangiectatic lesions in other parts of the gastrointestinal tract, a partial gastrectomy was performed (Ericsson) Jan. 27, 1955: At *laparotomy* no distinct lesions were visible on the stomach or the intestines. Nothing abnormal was found on palpation. The vessels to the part of stomach to be removed were ligated. The stomach was opened. Very little could be seen, no typical telangiectases. The mucous membrane was, however, quite thick. The distal part of the stomach was removed well above the limit observed at gastroscopy. Duodeno-gastrostomy was performed.

Post-operative course uneventful. Discharged two weeks later; hemoglobin 85 per cent (11.6 g %), erythrocytes 4.4 mill. Since operation he has been in an excellent condition and had no further bleeding. Examined at hospital 8 months later: hemoglobin 86 per cent, erythrocytes 4.1 mill., roentgenologic examination showing "a normally functioning stomach with signs of gastritis". Fifteen months after operation the boy is still in good general condition and has had no further bleeding.

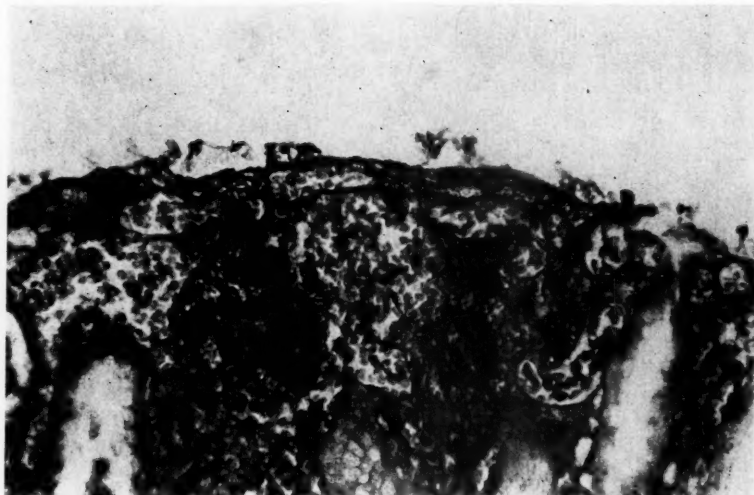


Fig. 2. Ectatic vessels of the mucosa. Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. $\times 240$.

Pathology (Ivemark):

Gross: The fixed specimen measured 7 cm along the lesser curvature and 10 cm along the greater curvature. In the mucosa in close proximity to the upper resection line scattered telangiectatic vessels were found. They were superficially located in the mucosa and measured 1–2 mm in width. They were found on the entire circumference of the stomach in a band measuring approximately 2.5 cm in greatest width.

Microscopic examination: In the mucosa, superficial areas of recent hemorrhage were located around collections of dilated capillaries just beneath the cylindrical epithelium of the surface (Figs. 2–3). These groups of enlarged capillaries were situated on the summits of the mucosal folds. Occasional vessels showed thickening of their walls. Otherwise the mucosa appeared normal. Apparently normal collections of arteries and veins were visible just inside the muscularis mucosae. The submucosa was edematous and very vascular. Most of the vessels had the appearance of abnormal large veins with irregular walls (Figs. 4–5). They were arranged in groups of three to four but did not show any evidence of hemangiomatous pattern. Occasionally, these large vessels were seen to pierce the muscularis mucosae and to branch into the mucosa in apparently a normal fashion. The muscular and serous layers were normal, except for a possible increase of the vascularity of the muscularis.

In summary, the pathologic findings included telangiectatic capillaries with recent hemorrhage of the superficial layer of the mucosa, edema of the submucosa, and dilatation and duplication of abnormal, predominantly venous channels of the submucosa. The findings were considered compatible with the diagnosis of Osler's telangiectasia of the stomach.

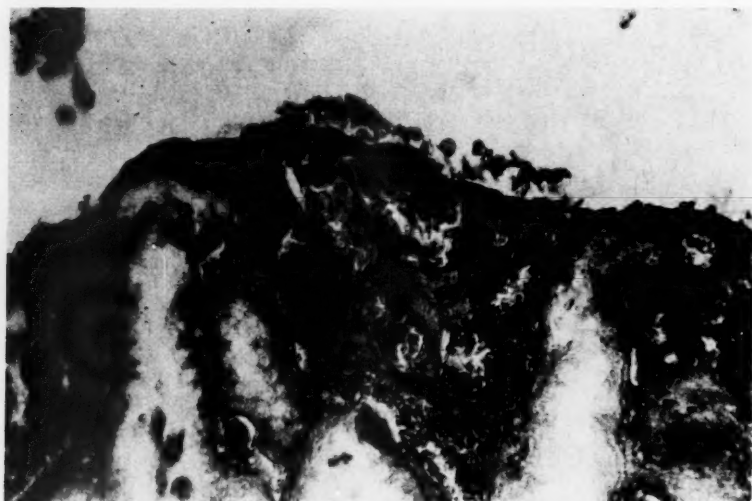


Fig. 3. Cluster of dilated vessels on summit of mucosal fold. Verhoeff's elastic tissue stain counterstained with van Gieson's stain. $\times 240$.



Fig. 4. Dilated and malformed vessels of the submucosa. Verhoeff's elastic tissue stain counterstained with van Gieson's stain. $\times 35$.



Fig. 5. Irregular wall of submucosal vessel. Verhoeff's elastic tissue stain counterstained with van Gieson's stain. $\times 240$.

Discussion

Heredity, of the dominant type, is almost generally accepted in the Rendu-Osler-Weber disease. However, several cases are published, lacking heredity (e.g. Osler, 1901). Fitz-Hugh (1931) has suggested that such cases could be explained as atavisms. In the family, studied by Dolowitz (1953), the disease never skipped a generation. In our case, there was no family history of telangiectases or suspected bleedings. As the lesions found both macro- and microscopically has been the same as in other cases of the Rendu-Osler-Weber disease, we feel that our case belongs to the same group.

Gastrointestinal bleeding in children has been subject to extensive studies by e.g., Brayton & Norris (1952). The cause of the bleeding could be demonstrated in the vast majority of their 428 cases, and the etiology was recorded as unknown in only 25 (6%). In their series there were two cases of "hemangiomata of intestine" and one of "generalized hemangioma with hematemesis". These cases are only briefly mentioned without any details. Hodgson & Kennedy (1954) stated that the lesions causing gross bleeding from the gastrointestinal tract in infants and children could be roentgenologically demonstrated in 90 per cent of their 246 patients. No case of telangiectasia was diagnosed in their series.

Gastrointestinal hemorrhage caused by telangiectases seems to be uncommon. In children it is rare.

A few adult cases have been described which have had typical gastrointestinal telangiectases without gastrointestinal bleeding, the lesions discovered at rectosigmoidoscopy (Hurst & Plummer, 1932) or at autopsy (Schuster, 1937).

Diagnosis: Telangiectases in the skin, nose or mouth of a patient suffering from gastrointestinal hemorrhages suggest the presence of telangiectatic lesions in the stomach or intestines. As the lesions are small, scattered over the mucosa and not protruding over the surface, roentgenologic examination of the stomach, a priori, seems to offer very little help to diagnosis. In the cases described by Brandel (1950), Shepherd (1953) and Williams & Brick (1955) the roentgenologic examination showed gastritis or question of ulcer. In our case big mucous folds were demonstrated, especially in the corpus region, which were supposed to be caused by telangiectases.

Endoscopy, only, may give a preoperative diagnosis. Since Renshaw (1939) reported the first case of telangiectasia demonstrated gastroscopically, this examination has been performed in a number of cases. In our case gastroscopy was of greatest value not only for diagnosis but also for determining the extension of the lesions.

Rectosigmoidoscopy should be performed in all these cases. The rest of the intestines cannot be examined endoscopically and roentgen examination cannot exclude telangiectases in that part of the gastrointestinal tract. Even at laparotomy the diagnosis may be extremely difficult or impossible, if there are no lesions visible on the outside of the gut, and no bleeding into its lumen going on.

Treatment: The only generally accepted treatment is replacement of the blood loss. No preoperative examination can give complete information about lesions in the gastrointestinal tract except those parts available to endoscopy. Small bleedings are no indication for operation, nor the presence of non-bleeding telangiectases found at routine endoscopy. Surgical treatment of gastric telangiectases can be discussed only in cases suffering from gross bleedings, threatening the patient's life or general condition. At operation it may be difficult to find the lesions, at least after ligation or temporary clamping of the vessels to the actual part of the stomach or intestines. Some adult cases have undergone two or three partial gastrectomies because of recurrent post-operative hemorrhages. (Shepherd, 1953; Williams & Brick, 1955). Even at post-mortem examination the telangiectases may be invisible (Dolowitz, 1953).

Prognosis: The mortality from the disease is reported to be about 4 per cent (Madden, 1934). Cases with telangiectases in the gastrointestinal tract seem to run a greater risk than cases with lesions localized only to the skin or nose.

Summary

A short review of the Rendu-Osler-Weber disease with report of a boy, five years old, suffering from recurrent gross bleedings from the gastrointestinal tract. Gastroscopy revealed gastric hemorrhagic telangiectases and a partial gastrectomy was performed. At follow-up examination 15 months later the patient is in good condition and has had no further bleeding. Discussion on diagnosis and treatment; endoscopy only may give the diagnosis; surgical treatment is recommended mainly in cases suffering from gross bleeding, threatening the patient's life or general condition.

Télangiectasie hémorragique gastrique chez un enfant.

Revue succincte de la maladie de Rendu-Osler-Weber et rapport du cas d'un garçon de 5 ans avec récurrence de fortes hémorragies gastrointestinales. La gastroscopie révèle de la télangiectasie hémorragique gastrique et on pratiqua une gastrectomie partielle. Un examen du malade 15 mois plus tard montra que son état général était bon, sans trace d'hémorragies nouvelles. Discussion du diagnostic et du traitement; il n'y a que l'endoscopie qui permette d'établir le diagnostic. Le traitement chirurgical se recommande surtout en cas de fortes hémorragies menaçant la vie ou l'état général du malade.

Blutende Magen-Teleangiectasie bei einem Kind.

Eine kurze Zusammenstellung des Schrifttums über die Rendu-Osler-Webersche Krankheit, mit anschliessendem Krankenbericht über den Fall eines 5jährigen Jungen, der an wiederholten massiven Blutungen vom gastro-intestinalen Trakt gelitten hatte. Mit Hilfe der Gastroskopie wurden blutende Teleangiectasien im Magen festgestellt und eine partielle Gastrektomie durchgeführt. Fünfzehn Monate später nachuntersucht, war der Patient frei von Haemorrhagien und in gutem Allgemeinzustand. Diagnose und Behandlung werden erörtert; nur die Endoskopie kann die Diagnose sicherstellen. Chirurgische Behandlung ist vor allem dann angezeigt, wenn es sich um Fälle mit heftigen Blutungen, welche das Leben oder das Allgemeinbefinden des Kranken bedrohen, handelt.

Telangiectasia gastrohorrágica de un niño.

Se revista sucintamente la enfermedad de Rendu-Osler-Weber y se relata el caso de un niño de 5 años de edad afecto de hemorragias gruesas recurrentes del conducto gastrointestinal. La gastroscopia reveló telangiectasias gastrohorrágicas y se ejecutó una gastrectomía parcial. El examen consecutivo 15 meses más tarde permitió comprobar que el paciente estaba en buena condición sin más síntomas de hemorragia. Discusión del diagnóstico y tratamiento; únicamente la endoscopia permite establecer un diagnóstico. El tratamiento quirúrgico está recomendado principalmente en casos de hemorragias gruesas que pongan en peligro la vida del paciente o su estado general.

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Ano-Rectal Abnormalities as a Congenital Familial Incidence

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Congenital abnormalities of the anus and rectum are reported as 1 in 5000 to 1 in 10,000 live births. They are somewhat more frequent in males than in females. Apart from the malformations of anus and rectum there are often in the same individual other anomalies. Their frequency is reported varying between 18 to 68 per cent.

Ano-rectal abnormalities among siblings are very unusual but their occurrence has been reported. Thus Suckling, in 1949, described 4 cases in 3 generations of the same family.

As familial occurrence of malformations of anus and rectum seems to be very rare, we hope that the following case of a family with such heredity may be of interest.

1: The mother was operated upon at the age of 3 weeks. Diagnosis: atresia ani + fistula rectovaginalis (Op. Rizzoli). She has had no further trouble.

2: Her first child was a female. Birth weight: 3270 g. She was admitted for observation to the medical department of the Central Hospital in Eskilstuna in July 1949 with the diagnosis: atresia ani congenit. cum fistula vaginalis. The fistula was thought to be functioning satisfactorily, but at the age of 6 months the baby died of ileus; this was verified by autopsy.

3: Her fifth child was our patient. A female, who was delivered by breech presentation in June 1956. Birth weight: 4360 g. On examination we found no anal canal but a fistulous opening of some millimeters diameter, ending in the perineum about 1 cm from the vagina. It was an anomaly that appeared to fit the classification of Gross and Ladd's type 3. Meconium passed through the fistula.

Within the first week the opening was dilatated without difficulty with Hegar bougies up to No. 10.

X-ray examination showed that a gap of about 1–2 cm existed between rectum and anus. As the way of the fistula in respect to the sphincter muscles could not now be determined and the fistula seemed to be functioning satisfactorily, it was decided that a further examination should be performed in about 3 months' time.

No other abnormalities have been found in this baby to date.

The other siblings—2 boys and 1 girl—and all other relatives have no known anomalies.

The parents are not blood relatives.

Summary

A case of atresia ani cum fistula rectoperinealis, where in the same family the mother and one sibling had similar anomalies, is reported. The mother was operated upon with good result. The sibling died of ileus at the age of 6 months.

Anomalies ano-rectales; incidence familiale congénitale.

Les auteurs rapportent des cas d'atrésie anale avec fistule rectopérinéale, anomalies similaires affectant dans la même famille la mère et un autre enfant. Réussite de l'opération chez la mère. L'autre enfant mourut d'iléus à l'âge de 6 mois.

Abnormalitäten des Anus und des Rectums, eine angeborene, familiengebundene Anomalie.

Krankenbericht über einen Fall von Atresia ani mit recto-perinealer Fistel, wobei ähnlichen Anomalien bei der Mutter und noch einem ihrer Kinder festgestellt wurden. Die Mutter wurde mit gutem Erfolg operiert. Das erste Kind starb im Alter von 6 Monaten an Ileus.

Anomalías anorectales de incidencia familiar congénita.

Relátase un caso de atresia del ano con fistula rectoperineal, existiendo en la misma familia anomalías análogas en la madre y un descendiente. La madre fué operada con buenos resultados. En cambio aquel murió de ileo a la edad de 6 meses.

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Monozygotic Twins, One with High Erythrocyte Values and Jaundice, the Other with Anaemia Neonatorum and No Jaundice

by JENS BERGSTEDT

In addition to the haemolytic disease of the newborn anaemias of another, often unknown origin occur and are denoted as anaemia neonatorum. In the latter conditions, signs of regeneration in the form of an increased number of nucleated red cells, leukocytosis, and enlargement of the liver and spleen are lacking. Anaemia neonatorum has been described by many authors, among them Vahlquist (6), Herlitz (1) and Uhrbrand *et al.* (7).

An account is given in this paper of a pair of monozygotic twin girls; one of them exhibited anaemia neonatorum at birth, and the other a high normal erythrocyte value. Herlitz reported two similar pairs of twins, and pointed out that the aforementioned difference in the number of red cells was probably due in part to the existence of placental anastomoses. Jaundice was present in none of his twins, whereas in the cases described here, jaundice was marked in the twin with a high erythrocyte count and inappreciable in the one with anaemia neonatorum. Klingberg *et al.* (2) has reported a similar case.

Case Reports

History.—The mother had a negative Wassermann reaction. Her twin pregnancy was not known before parturition. When twin I had been born, cessation of the cord pulsations was awaited before severing it. Since, after about 15 minutes, no change had occurred in the pulsations, the cord was ligated. Shortly afterwards, twin II was born and was seen at once to be remarkably pale. The placenta was inspected by the obstetrician, who found it to be monozygotic and therefore made the "milk test". On injection of milk into one of the cords, both placentas became filled with milk.

Twin I.—Birth weight 3030 g. Remitted to Kronprinsessan Lovisas Barnsjukhus on the 3rd day of life. On admission, slight jaundice was present; the liver and spleen were palpable one fingerbreadth below the costal margin in the mamillary line. The umbilicus was slightly red and swollen at the cranial margin; there was no discharge. The blood values on admission were: haemoglobin 23.6 g/100 ml, R.B.C. 5.9 million/

mm³, colour index 1.32, W.B.C. 8900/mm³. The faeces were moderately greenish-yellow, granular and mucoid.

An alcohol compress was applied to the umbilicus, and oral achromycin therapy was given in view of the coincident dyspepsia. The patient's general condition was unaffected throughout her stay in hospital; she sucked well from the start and did not vomit. The gain in weight was satisfactory. On the 4th day after admission, the appearance of the umbilicus and of the faeces was normal; achromycin therapy was therefore discontinued.

Jaundice rapidly became more profound from the 3rd day of life, and was maximal two days later. The quantitative serum bilirubin was 23.5 mg/100 ml, no direct bilirubin was demonstrable with the Jendrassik and Grof test. The direct van den Bergh reaction was negative. The icterus index was 1:120. Harrison test on the urine: traces of bilirubin. The patient continued to be deeply jaundiced for some time; on the 14th day of life the icterus index was 1:60. The differential cell count, osmotic resistance, and serum sodium and chlorides were within normal limits (see Table 1). The M.S.R. was 1 mm/hr on the 7th and 14th day of life, respectively. The patient was sent home in good condition on the 16th day of life. She then weighed 2950 g; she was moderately jaundiced, the liver was palpable one fingerbreadth below the costal margin in the mamillary line, and the spleen at the level of the costal margin.

At follow-up examination when the patient was 5 months old, development was normal and she weighed 6400 g; no jaundice was present and nothing pathologic was found in the internal organs. For blood laboratory data, see Table 1.

Twin II.—Birth weight 1810 g. Remitted to Kronprinsessan Lovisas Barnsjukhus a few hours after birth. On admission, she was pale but not generally affected; there was no jaundice nor any evidence of bleeding into the skin or mucous membranes. The liver was palpable a half-fingerbreadth below the costal margin in the mamillary line, and the spleen at the level of the costal margin. The blood values on admission were: haemoglobin: 13.6 g/100 ml, R.B.C. 3.9 million/mm³, colour index 1.01, reticulocytes 4.9 %, and prothrombin index 92. The faeces were of normal colour.

The patient was nursed in a cot heated with hot-water bottles. She sucked well from a teat from the beginning, gained satisfactorily in weight and did not require oxygen administration. No form of blood transfusion was given. The differential cell count and osmotic resistance of the red cells were within normal limits. Slight jaundice was present from the 3rd to 11th day of life; the maximum icterus index was 1:30. The Harrison test on the urine was negative with maximal jaundice, and other urine analyses showed nothing pathologic. The haemoglobin level fell slowly to 9.6 g/100 ml at 6 weeks of age, when the patient was sent home. She was given oral iron therapy from the 4th week of life.

Follow-up examination at 5 months of age showed the general condition to be good, and nothing pathologic was found in the internal organs. For blood laboratory data, see Table 1.

Serologic reactions (performed at the Rh Laboratory, State Chemico-Legal Laboratory).¹ Blood groups:

Father: A₂ M N P + Rh(+), type Rh₁rh

Mother: O N P - Rh(+), type Rh₁rh

Twins: O M N Rh(+), type Rh₀

¹ I am indebted to Docent B. Broman for these determinations.

TABLE I
Blood laboratory data.

	TWIN I				TWIN II			
Age	3 days	7 days	14 days	5 mths	1 day	5 days	15 days	5 mths
Haemoglobin, g/100 ml	23.6	21.5	19.3	10.7	13.3	13.0	12.4	9.3
R.B.C./mm ³	5,900,000	6,000,000	5,400,000	3,800,000	3,900,000	3,700,000	3,800,000	3,600,000
Nucleated red cell/mm ³	0	0	0	0	2,200	0	0	0
W.B.C./mm ³	8,900	11,000	8,200	11,000	22,300	11,200	8,700	11,600
Differential count, %								
Myelocytes	0	—	—	0	1	0	0	0
Young neutrophils	2	—	—	0	1	0	0	0
Stab neutrophils	3	—	—	0	5	5	1	1
Segmented neutrophils	49	—	—	28	69	47	30	28
Eosinophils	5	—	—	3	2	5	5	6
Lymphocytes	38	—	—	64	20	41	56	62
Monocytes	3	—	—	3	2	2	5	3
Plasmacells	0	—	—	2	0	0	3	0
Reticulocytes, %	—	—	—	—	4.9	4.2	1.4	3.0
Fragility of erythrocytes								
Haemolysis starts, % NaCl		0.46				0.46-0.44		
Haemolysis complete, % NaCl . .		0.30				0.28		
Serum chlorides, mEq/l		116				113		
Serum sodium, mEq/l		155				155		
Prothrombin index, %	89	69	92	—	92	92	—	—
Icterus index	—	1:120	1:60	—	—	1:28	—	—

No irregular agglutinins were demonstrated in the mother's serum, and the Coombs' test was also negative with the babies' blood cells. In view of the blood group combinations of the parents and of both twins, and on the basis of the incidence figures for twins in Scandinavia, the probability of their being monozygotic can be calculated to exceed 80 per cent.

Discussion

The nature of the placentas indicates, with a high degree of probability, that the twins were monozygotic. Further evidence is afforded by the existence of a direct communication between their blood circuits via the placentas, a fact shown by Schatz (5) already at the end of the 19th century to apply in monozygotic twins. The serologic tests also indicate that these twins were monozygotic.

The larger twin I had probably received a considerable quantity of blood from the smaller twin II. After the birth of twin I, it can be presumed that not only her own blood, but also blood from twin II, was pumped back from the placenta. This would explain the considerable difference between the twins with respect to the erythrocyte count, it being lower in twin II. Seip (4) stated the reverse to be the rule in twins, since complete contraction of the uterus after the last birth gives the last-born an extra supply of blood.

On admission, twin I had no clinical signs of dehydration that could have explained the high erythrocyte count which, according to Lippmann (2) lies on the upper borderline of the normal range. Moreover, this count remained on a high level during the whole time she was in hospital. The high colour index on admission may to some extent have been due to disturbance of the haemoglobin determination (determined photometrically as oxyhaemoglobin) by jaundice.

Twin II had unquestionable anaemia already a few hours after birth. The mother's negative W.R., the good condition of the infant and the absence of bleeding into the skin or mucous membranes, as well as the results of the serologic tests, argue against congenital syphilis, sepsis, haemorrhage or erythroblastosis as the cause of anaemia.

The difference between the degree of jaundice in these twins is remarkable. As a rule, jaundice is more profound and more prolonged in premature than in full-term infants. Schäfer (4) has shown, by means of bilirubin tolerance tests, that the former have relative hepatic insufficiency as compared to the latter. Twin II exhibited inappreciable jaundice, whereas twin I was deeply jaundiced. The same conditions applying in twin I argue against congenital syphilis, sepsis, and erythroblastosis as the responsible factors. The possibility of biliary occlusion is not substantiated by the normal colour of the faeces and the benign course. The most likely cause of the marked jaundice in twin I seems to be the high erythrocyte count

which, through physiologic haemolysis, primarily gave rise to the marked increase in the bilirubin content of the blood. Secondly, relative hepatic insufficiency undoubtedly contributed to the prolonged course, in accordance with the facts stressed by Vahlquist and by Schäfer, among others.

Summary

An account is given of a pair of monozygotic twin girls with established anastomoses between the two placentas. A considerable difference in the red cell count was present at birth; the first-born, larger twin had high erythrocyte values and the last-born, underweight had anaemia neonatorum. Marked jaundice subsequently appeared in the first-born, whereas it was inappreciable in the last-born. The presence of Rh or irregular agglutinins was ruled out by serologic tests. It is suggested that the larger twin I received blood from the smaller twin II via the placentas, and that the difference in the degree of jaundice is a direct result of the difference in the red cell count.

Jumelles monozygotes avec polyglobulie et ictère chez l'une et anémie des nouveau-nés sans ictère chez l'autre.

L'auteur décrit une paire de jumelles monozygotes avec anastomoses entre les deux placentas. A la naissance, il y avait une différence considérable de la numération globulaire rouge; la première née, la plus grosse, avait de la polyglobulie et la deuxième, débile, avait de l'anémie. L'ictère se développa ensuite, forte chez la première née et inappréciable chez la seconde. Les test sérologiques montrèrent l'absence de facteur Rh ou d'agglutinines irrégulières. L'auteur suppose que la jumelle la plus grosse reçut du sang de la plus petite par la voie placentaire et que la différence du degré de l'ictère est due directement à la différence de la numération globulaire rouge.

Eineiige Zwillinge, der eine mit Polyglobulie und Icterus, der andere mit Anaemia neonatorum ohne Icterus.

Beschreibung eines Paares von eineiigen Zwillingen weiblichen Geschlechts, mit nachgewiesenen Anastomosen zwischen den Placentae. Es bestand zur Zeit ihrer Geburt ein beträchtlicher Unterschied in der Zahl der roten Blutkörperchen; der erstgeborene, grössere Zwilling hatte Polyglobulie, während der zweite mit Untergewicht, Anaemia neonatorum aufwies. Ausgesprochener Icterus entwickelte sich daraufhin bei dem erstgeborenen Mädchen, während das andere anscheinend frei davon blieb. Die Anwesenheit von Rh oder unregelmässigen Agglutininen konnte mit Hilfe von serologischen Proben ausgeschlossen werden. Es wird die Ansicht ausgesprochen, dass der grössere Zwilling auf dem Weg über die Placenta Blut von dem kleineren Zwilling bezogen hatte und dass der Unterschied in der Intensität des Icterus ein direktes Ergebnis des Unterschiedes in der roten Blutkörperchenzahl gewesen ist.

Gemelas monocigóticas, la una con policitemia e ictericia, la otra con anemia del neonato sin ictericia.

Relátase el caso de dos gemelas monocigóticas con anastomosis establecidas entre las dos placentas. Obsérvese una considerable diferencia hemacitométrica roja al

nacimiento; la primera niña en nacer, la gemela de mayor tamaño, presentaba policitemia, y la segunda, de peso insuficiente, presentaba anemia del neonato. Desarrollóse una ictericia marcada en la primera nacida, mientras fué inapreciable en la última. Quedó excluida la presencia de Rh o aglutininas irregulares al examinarse los sueros. Se sugiere que la gemela mayor recibió sangre de la menor por conducto de las placentas y que la diferencia en el grado de ictericia resulta directamente de la diferencia hematométrica roja.

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SUMMARIES OF SUPPLEMENTS

Changes in Body Water Compartments during Growth

by BENT FRIIS-HANSEN

(Summary of Supplement 110)

This Supplement contains data on the magnitude of the various body water compartments during growth in normal infants and children. Some of the data have been published earlier by the author but additional measurements are now given. The series consisted of 93 subjects from 1 day to 16 years of age.

Total body water, by definition equal to the volume of distribution of deuterium oxide (heavy water) was measured in 73 children. *Extracellular water*, by definition equal to the volume of distribution of the thiocyanate ion, was measured in 51 children. *Intracellular water*, by definition equal to the total body water less the extracellular water, was measured in 31 subjects.

The figures for *total body water* were submitted to statistical analysis in order to study the relationship between the total body water and the age, weight, height, and surface area of the subjects. The closest correlation was found between total body water and a combination of weight and height (relative standard deviation = 7.9%). The correlation between total body water and weight was of the same order of magnitude (relative standard deviation = 8.0%). It was concluded that for clinical purposes, the simplest estimate of total body water is that obtained by calculation in per cent of body weight, thus, 0–11 days 77.6%, 11 days–6 mths. 72.2%, 6 mths.–2 yrs. 59.5%, 2 yrs.–7 yrs. 63.1% and 7 yrs.–16 yrs. 58.4%. Since no close correlation was found, no normal values could be stated for any given child. For purposes of research body water has to be measured directly whenever accurate values are needed.

The values for *extracellular water* were analysed in the same way. No close correlation was found between this parameter and the measurements mentioned above. The relative standard deviation for the correlation between extracellular water and weight was 15.2%. The following values were found in the different age groups: 41.6, 33.7, 26.2, 24.7, and 19.9 per cent. Extracellular water expressed as litres per sq.m. of surface was fairly

constant within the age groups; thus 6.7, 5.8, 5.9, 5.9, and 5.6 litres per sq.m.

The volume of *intracellular water* was calculated and analysed statistically as for total body water and extracellular water. When intracellular water was related to the body weight, a relative standard deviation of 20.8% was found. Expressed in per cent of body weight, the following values were found for the different age groups: 34.8, 37.9, 34.7, 39.9, and 46.7 per cent. When expressed in litres per sq.m. surface area, the intracellular water increases gradually from 5.6, 6.5, 7.5, and 9.3 to 14.7 litres per sq.m.

The significance of the changes in total body water, extracellular water, and intracellular water during growth are discussed, and mainly ascribed to 1) a relative increase in the proportion of cells in most tissues at the expense of extracellular fluid, 2) a disproportionally greater development of organs such as muscles that contain a high proportion of intracellular water, and 3) a varying amount of adipose tissue in the body.

Capillary Erection and Lung Expansion

An Experimental Study of the Effect of Liquid Pressure Applied to the Capillary Network of Excised Fetal Lungs

by S. JÄYKKÄ

(Summary of Supplement 112)

The opinion is presented that a previously uninvestigated factor, capillary erection, plays an important part in effecting lung expansion in the newborn infant. The respiratory part of the lung is the apparatus in which capillary erection occurs and the erection is effected by an increase in liquid pressure in the pulmonary artery.

The opinion is based upon histological investigations and upon the following model experiments:

The architecture of primary atelectasis has been studied by examining the general course of the capillary network which has been rendered visible by injecting india ink into the pulmonary artery. The findings are in agreement with those of Potter who has stated that a lung in primary atelectasis may be compared to a crumpled sack. In this case atelectasis has been understood to mean the architecture of the fetal lung at term before any aeration or expansion has occurred.

The opening-up of the atelectatic lung is considered to involve its extension as a result of the active erection of the capillary network. Evidence in support of this opinion has been obtained by studying various stages of expansion in the same preparation. Thus the straightening-out of the crumpled sack effects the expansion of the respiratory part of the lung.

Expansion experiments have been performed on lungs of stillborn human and lamb fetuses. The following possibilities have been examined:

1. Lung expansion effected by an air pressure difference in the respiratory passages. This method is termed air inflation.
2. Lung expansion effected by liquid pressure in the capillary network. This method is termed erectile expansion.
3. Lung expansion effected by air inflation and erectile expansion concurrently.

The results of the expansion experiments show that the air inflation effects an expansion which is characterized by a microscopical picture showing globular saclike hyperdistended air spaces primarily in the distal conducting part of the lung. A similar condition of the lung results from the child's own respiratory efforts in cases where the erectile forces in the capillaries have been weak or nonexistent.

Liquid pressure acting through the pulmonary artery produces in the respiratory part a condition which exactly corresponds in its microanatomical features to a normal aerated lung.

Air inflation and erectile expansion together produce a picture which is similar to that effected by erectile expansion alone. By increasing the air pressure difference it is possible to change the balance between the air inflation and erectile expansion so that features appear in the microscopical picture which are typical of a lung expanded by air inflation alone.

Both when effected experimentally or by the child's own respiratory movements, air inflation appears to hinder attainment of the normal structure by the capillary network by stretching the capillaries and by forcing them to conform to the hyperdistention of the air spaces. The stretching of the capillaries appears to prevent their bulging into the adjacent air spaces.

PROCEEDINGS OF PEDIATRIC SOCIETIES

Section of Pediatrics and School Hygiene of the Swedish
Medical Society

Meeting at Borås, September 22—23, 1956.

B. Söderling and A.-L. Bergström: Corticosteroids in Paediatric Practice.

Cortisone, hydrocortisone, and prednisone have been in increasing use during the past 4 years at the Paediatric clinic, Borås, in both in-patients and out-patients. A large number of children have been treated, mostly for fairly short periods. The chief indications have been as follows.

1. Troublesome allergies, in particular infantile eczema and chronic asthma.
2. Severe acute and sub-chronic conditions, in combination with antibiotics.
3. Conditions of 'stress' in children with psychosomatic symptoms or anxiety states.
4. Grave surgical conditions, such as severe toxic peritonitis, extensive burns, etc.

The groups are not clearly defined, there being considerable overlapping of cases. The 'stress' factor must always be borne in mind in painful, frightening, and chronic illness. The beneficial affect of the drugs in 'stressed' children may, perhaps, be ascribed to a 'latent allergy', however.

DISCUSSION.—*C. Thorén*. It has been feared that in prolonged corticosteroid therapy there is a risk of causing atrophy of the adrenal cortex unless this is stimulated by short periods of ACTH. Pronounced adrenal atrophy has been noted at the Crown Princess Louise Hospital for Children in cases of leukaemia treated with cortisone during several months. On microscopical examination this has been found to be general and unspecific.—*T. Torstensson*. Prolonged ACTH and cortisone treatment of a patient with alopecia, previously treated by a hypophyseal implant, produced no convincing effect.—*K. Holmdahl*. The same good effect of the cortisone preparations in allergic illness in children is experienced at an child-allergy out-patient clinic. Not only the severe acute and chronic asthmas but also the pollinoses and dermatoses are nearly always improved. In the two last-named, local treatment is usually satisfactory. It must, however, be stressed that our knowledge of the late effects of this drug is little. It is known that it occupies a key position in the endocrine orchestra; and it is also a fact that adults may occasionally show signs of skeletal disease, sexual disturbance, etc. It would appear not unlikely that the administration of hormones often necessary for many years in severe, chronic asthma may have deleterious side effects on the growing organism. So long as uncertainty exists I believe that great caution should be exercised. Prolonged cortisone therapy should be reserved for severe cases that do not

respond to other treatment, and the dose should be carefully 'titrated': thus 2.5 mg. of 'delta'-cortisone is often quite enough. As soon as symptom-free periods appear the dose should be reduced or the drug completely excluded.

T. Axelsson and T. Torstenson: Two cases of degenerative myopathy.

A brief review was followed by an account of two cases interpreted as progressive infantile spinal myatrophy.

Case 1. A boy, now aged 3 years, who began to show at 7 months loss of tendon-reflexes, muscular hypotonia, paresis (chiefly of the sphincters, legs, and back), with no signs of pyramidal-tract lesion, no mental involvement, and no sensory disturbance. Muscle-biopsy also suggested the above diagnosis. The case is interpreted as being one of infantile progressive muscular atrophy of Werdnig-Hoffman.

Case 2. A girl, now aged $2\frac{1}{2}$, in whom signs of paresis were first observed at the age of 10 days. At present the signs are marked muscular hypotonia, absence of tendon reflexes, partial paralysis (chiefly sphincters and legs). Lumbar puncture gave no abnormal findings, and the W. R. was negative. There was no sensory disturbance, no signs of pyramidal-tract involvement, and no mental disturbance. Muscle biopsy also suggested the above diagnosis. 'Delta-cortril' was given for a period of 3 weeks, during which the knee and ankle jerks returned and remained unchanged during the following 6 months. It is not certain, however, whether this was *post hoc ergo propter hoc*. The diagnosis of infantile myatrophy of Oppenheimer was made.

DISCUSSION.—H. Jelke. We have had a similar case in a 6-year-old girl, now a complete invalid but with normal intellect. In her case the VIIth-nerve nuclei are involved, with resultant facial paralysis including paralysis of chronic suppurative conjunctivitis due to the lagophthalmos, and intermittent keratitis, which is totally resistant to all treatment. The correct diagnosis of degenerative myopathy at an early stage is often difficult. An example is the case of a 4-year-old girl with progressive hypotonia and weakness starting at the age of one year. The tentative diagnosis of amyotonia congenita (probably of Oppenheimer's type) was to some extent supported by the biopsy findings. Three years later, however, she developed striking pseudo-hypertrophy, chiefly of the calves, which clinched the diagnosis of progressive muscular dystrophy, a condition which is sometimes congenital. One has the impression that in assessing these cases the pathologists are almost too willing to confirm the clinical diagnosis.

S. Joachimsson: Pulmonary apoplexy?

Three cases are described of massive pulmonary haemorrhage with no signs of inflammation in new-born infants, in which this was the only finding at necropsy. The pathologist called the condition *apoplexia pulmonum*, presumably in analogy to *apoplexia suparenalis*. The aetiology and pathogenesis are discussed.

P. Zetterquist: Icterus gravis of prematurity.

It has become increasingly clear during recent years that icterus gravis of the newborn occurs not only in haemolytic disease but also in other states. This is particularly true in premature infants. Six cases of kernicterus in premature infants are de-

scribed, of which 4 occurred during a calendar year in a series of 28 infants with a birth weight of less than 2,500 g. The babies were reared by routine methods, but were given large doses of water-soluble synthetic vitamin K (Synkavit) intramuscularly (10 mg. per day during at least one week). Jaundice appeared at 4.5 days, and was associated with the same neurological signs as those seen in bilirubin encephalopathy of other aetiology. Four of the infants died within a few days, and the other two are mentally retarded and show central motor disturbance of extrapyramidal type. In premature infants encephalopathy develops at relatively low bilirubin levels. This has been claimed to be due as a sequel to immaturity of the nerve cells or injurious occurrences (such as anoxia) during the first days of life. The high dosage of synthetic vitamin K in these cases was probably highly significant in the development of the icterus gravis. The only conceivable treatment of icterus gravis at present is replacement transfusion, but the indications for this and the technique present difficulties in this late form of jaundice in premature infants.

B. Söderling: The traditional concept of prematurity, a scientific misconception.

(To be published elsewhere).

ANNOUNCEMENTS

The Responsibilities of the Medical Profession in the Use of X-Rays and Other Ionizing Radiation

Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

1. The United Nations General Assembly, being aware of the problems in public health that are created by the development of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radiotherapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

2. Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

3. It is now accepted that the irradiation of human beings, and particularly of their germinal tissues, has certain undesirable effects. While many of the somatic effects of radiation may be reversible, germinal irradiation normally has an irreversible and therefore cumulative effect. Any irradiation of the germinal tissues, however slight, thus involves genetic damage which may be small but is nevertheless real. For somatic effects there may however be thresholds for any irreversible effects, although if so these thresholds may well be low.

4. The information so far available indicates that the human race is subjected to natural radiation,¹ as well as to artificial radiation due to its medical applications, to atomic industry and its effluents and to the radioactive fall-out from nuclear explosions. The Committee is aware of the potential hazards that such radiation involves, and it is collecting and examining information on these subjects.

5. The amount of radiation received by the population for medical purposes is now, in certain countries, the main source of artificial radiation and is probably

¹ The radiation due to natural sources has been estimated to cause between 70 and 170 millirem of irradiation to the gonads per annum in most parts of certain countries in which it has been studied, although higher values are found locally in some areas. See the reports "The hazards to man of nuclear and allied radiations" published by the United Kingdom Medical Research Council in June 1956, in which also the millirem is defined; and from information submitted to the Committee.

about equal to that from all natural sources. Moreover, since it is given on medical advice, the medical profession exercises responsibility in its use.

6. The Committee appreciates fully the importance and value of the correct medical use of radiation, both in the diagnosis of a large number of conditions, in the treatment of many such diseases as cancer, in the early mass detection of conditions such as pulmonary tuberculosis, and in the extension of medical knowledge.

7. Moreover, it appreciates fully the contribution of the radiological profession, through the International Commission on Radiological Protection,¹ in recommending maximum permissible levels of irradiation. As regards those whose occupation exposes them to radiation, the establishment of these levels depends on the view that there are doses which, according to present knowledge, do not cause any appreciable body injury in the irradiated individual; and also on the consideration that the number of people concerned is sufficiently small for the genetic repercussions upon the population as a whole to be slight. Whenever exposure of the whole population is involved, however, it is considered prudent to limit the dose of radiation received by germinal tissue from all artificial sources to an amount of the order of that received from the natural background radiation.

8. It appears most important therefore that medical irradiations of any form should be restricted to those which are of value and importance, either in investigation or in treatment, so that the irradiation of the population may be minimized without any impairment of the efficient medical use of radiation.

9. The Committee is consequently anxious to receive information through appropriate governmental channels as to the methods and the extent by which such economy in the medical use of radiation can be achieved, both by avoiding examinations which are not clearly indicated and by decreasing the exposure to radiation during examinations, particularly if the gonads, or the foetus during pregnancy lie in the direct beam of radiation. It seeks, in particular, to obtain information as to the reduction in radiation of the population which might be achieved by improvements in instrument design by fuller training of personnel, by local shielding of the gonads, by choosing appropriately between radiography and fluoroscopy, and by better administrative arrangements to avoid any necessary repetition of identical examinations.

10. The Committee also seeks the co-operation of the medical profession to make possible an estimate of the total radiation received by the germinal tissue of the population before and during the child-bearing age. It considers it to be essential that standardized methods of measurement, of types at present available, should be widely used to obtain this information and it emphasizes the value of adequate records, maintained by those using radiation medically, by the dental profession, and by the responsible organizations in allowing such radiation exposure to be evaluated. The Committee is convinced that information of this type will make it possible to decrease the total medical irradiation of the population while preserving and increasing the true value of the medical uses of radiation.

¹ See the report of the International Commission on Radiological Protection (published in the *British Journal of Radiology*, Suppl. 6, of December 1954, in the *Journal français d'électro-radiologie*, No. 10, of October 1955, etc., and revised in 1956).

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